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(54) Title: A NOVEL BIOADHESIVE DRUG DELIVERY SYSTEM BASED ON LIQUID CRYSTALS

(57) Abstract

A drug delivery system containing a liquid crystalline phase such as a cubic, a hexagonal, a reverse hexagonal, a lamellar, a micellar and a reverse micellar liquid crystalline phase. The compositions are unique in that they, as delivery system, contain A) a substance which is capable of generating a liquid crystalline phase and providing suitable biopharmaceutical properties like e.g. suitable release of the active substance and bioadhesive properties, and B) at least another substance which without having any substantially negative effect on the biopharmaceutical properties provided by the substance mentioned above under A) either takes part in the formation of a liquid crystalline phase or dilutes the proportion of liquid crystalline phase in the composition while still maintaining suitable biopharmaceutical properties and a suitable storage stability. Examples of substances A) are fatty acid esters like e.g. glycerylmonooleate and glycerylmonolinoleate and examples of substances B) are e.g. structurants like phospholipids and tocopherols and/or pharmaceutically acceptable excipients.

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A NOVEL BIOADHESIVE DRUG DELIVERY SYSTEM BASED ON LIQUID CRYSTALS

The present invention relates to a drug delivery system containing a liquid crystalline phase such as a cubic, a hexagonal, a reverse hexagonal, a lamellar, a micellar and a reverse micellar liquid crystalline phase. The compositions are unique in that they as delivery system contains A) a substance which is capable of generating a liquid crystalline phase and providing suitable biopharmaceutical properties like e.g. suitable release of the active substance and bioadhesive properties, and B) at least another substance which without having any substantially negative effect on the biopharmaceutical properties provided by the substance mentioned above under A) either takes part in the formation of a liquid crystalline phase or dilutes the proportion of liquid crystalline phase in the composition while still maintaining suitable biopharmaceutical properties and a suitable storage stability.

The present invention also relates to a pharmaceutical composition for administration of an active substance to or through a damaged or undamaged skin or mucosal surface or to the oral cavity including the teeth of an animal such as a human. The composition is particularly suited for administration of substances which have a very low water solubility and which are to be supplied in an effective amount in a localized region over a period of time.

The present invention also relates to a pharmaceutical composition for administration of an active substance to a mammal such as a human. The composition is unique in that it contains i) a substance which together with a liquid medium such as e.g. water is capable of forming a liquid crystalline phase at room temperature and ii) a so-called structurant which is capable of participating in the formation of the liquid crystalline phase at room temperature. Such compositions are especially useful when it is desired to reduce the concentration of the substance mentioned under i) above in the composition without any significant or negative influence on the biopharmaceutical properties of the composition.

Furthermore, the invention also relates to a pharmaceutical composition in which it is possible to incorporate relatively large amount of certain pharmaceutically acceptable excipients without significantly changing the biopharmaceutical properties of the composition.

Background of the invention

From WO 95/26715 it is known that certain fatty acid esters have bioadhesive properties which are suitable for use in pharmaceutical compositions. Furthermore, WO 97/13528 (published on 17 April 1997 corresponding to the priority date of the present application) discloses pharmaceutical compositions containing active drug substances having a relatively low solubility

in water at a pH of between 3.0 and 9.5 such as, e.g., between 3.2 and 9.3, between 3.4 and 9.1 or between 3.6 and 9 and having a relatively high release rate of the active drug substance for a suitable and sufficiently long period of time.

The pharmaceutical compositions disclosed in the above-mentioned international patent application are all based on a content of a fatty acid ester which is sufficient to enable a formation of a liquid crystalline phase either in the composition itself or in situ after application of the composition in the form of a so-called precursor composition.
For various reasons (such as, e.g., i) formulation considerations such as, e.g., viscosity, dosage form aspects etc., ii) patient acceptability considerations such as, e.g., appearance, taste, tolerability etc.) it may be desirable to reduce the amount of fatty acid ester present in the pharmaceutical compositions. However, the present inventor has found that a reduction in the content of a fatty acid ester, i.e. a substance which is capable of generating a liquid crystalline phase together with a suitable liquid medium, is not a simple routine for a person skilled in the art if the biopharmaceutical properties of the compositions (such as, e.g., release properties, bioadhesive properties and appropriate storage stability properties) still have to be maintained. In general, especially stability properties have been observed if such excipients which normally is used within the pharmaceutical field have been added to the liquid crystalline phase.

Notably, in the case where an aqueous medium serves as a liquid medium with which the fatty acid ester forms the liquid crystalline phase the inventor has, however, observed difficulties in reducing the concentration of fatty acid ester in the composition below a certain limit (for glycerylmonooleate. The limit has been found to be about 60-65% by weight in non-precursor compositions) without getting a two phase system, e.g. a cubic phase in excess water.

Disclosure of the invention

In searching for substances which may at least partly function as a suitable substitute for a liquid crystalline phase-forming substance like e.g. a fatty acid ester in such a composition, the inventor has now surprisingly found that substances which not necessarily are able to form a liquid crystalline phase together with water at room temperature but which together with a fatty acid ester and a liquid medium is capable of forming a liquid crystalline phase are capable of substituting the fatty acid ester and still retaining the required properties with respect to e.g. release of active substance, bioadhesion, solubility of active substance in the fatty acid ester component etc. Such substances are in the following denoted "structurants" due to the observation that such substances most likely together with the liquid crystalline phase-forming substance like e.g. the fatty acid ester participate in the formation of the liquid crystalline phase structure and, thus, impart a liquid crystalline phase structure to the composition. A structurant

is, accordingly, not a substance which merely is enveloped or enclosed in the composition and which, accordingly, would result in a dilution of the crystalline liquid medium which in turn may result in a composition having a reduced bioadhesiveness compared with the parent composition where no substitution of the liquid crystalline phase-forming substance content has taken place. A structurant is capable of ensuring that a substitution of a certain amount of the fatty acid ester does not result in a deterioration of the content and pharmaceutical function of the liquid crystalline phase formed by e.g. a fatty acid ester and a liquid medium.

Thus, the invention relates to a pharmaceutical composition for administration of an active substance to or through a nail or a damaged or undamaged skin or mucosal surface of a mammal (such as an animal or a human), the composition comprising

i) a first substance which is the active substance,

ii) an effective amount of a second substance which, together with a liquid medium, is capable of generating a liquid crystalline phase in which the constituents of the composition are enclosed, the liquid crystalline phase being selected from the group consisting of: a cubic, a hexagonal, a reverse hexagonal, a lamellar, a micellar and a reverse micellar liquid crystalline phase,

iii) a structurant which together with said second substance and a liquid medium is capable of forming a liquid crystalline phase selected from the group consisting of: a cubic, a hexagonal, a reverse hexagonal, a lamellar, a micellar and a reverse micellar liquid crystalline phase; and

iv) optionally, a liquid medium which is substantially homogeneously distributed in the composition,

the composition either being one in which the liquid crystalline phase has been generated by the second substance and the structurant together with a sufficient amount of a liquid medium originally present in the composition, or the composition being in a precursor form in which the second substance and the structurant have not generated the liquid crystalline phase, but are capable of forming the liquid crystalline phase <u>in situ</u> with moisture from the surface on which the composition is applied, the moisture in this case constituting at least part of the liquid medium,

the pH of the liquid crystalline phase being in the range of 3.0-9.5 such as, e.g., 3.2-9.3, 3.4-9.1 or 3.6-9.0, determined as described herein,

the active substance having

i) a first solubility in the liquid crystalline phase of at the most 20 mg/g at 20°C, and

ii) a second solubility in water of at the most 10 mg/ml at 20°C, the water, where applicable, being buffered to a pH in a range of 3.0-9.5 such as, e.g., 3.2-9.3, 3.4-9.1 or 3.6-9.

International patent application No. PCT/DK96/00437, published on 17 April 1997, discloses a composition containing 5% by weight of acyclovir and 95% by weight of a glycerylmonooleate/water/lecithin (55/35/10% w/w) formulation, wherein the glycerylmonooleate product is DIMODAN® GMO-90 and the lecithin is Epikuron 200, and a composition containing 5% by weight of acyclovir and 95% by weight of a glycerylmonooleate/water/d-α-tocopherylpolyethyleneglycol 1000 succinate (65/35% w/w glycerylmonooleate/water plus 5% w/w d-α-tocopherylpolyethyleneglycol 1000 succinate), wherein the glycerylmonooleate product is DIMODAN® GMO-90.

Therefore, for states in which the present application is co-pending with a national phase of the above international patent application (this is expressed in the claims as "where applicable"), the following proviso applies to the scope of the present application: the composition is not one consisting of either a) 5% by weight of acyclovir and 95% by weight of a glycerylmonooleate/water/lecithin (55/35/10% w/w) formulation, wherein the glycerylmonooleate product is DIMODAN® GMO-90 and the lecithin is Epikuron 200, or b) 5% by weight of acyclovir and 95% by weight of a glycerylmonooleate/water/d-α-tocopherylpolyethyleneglycol 1000 succinate (65/35% w/w glycerylmonooleate/water plus 5% w/w d-α-tocopherylpolyethyleneglycol 1000 succinate), wherein the glycerylmonooleate product is DIMODAN® GMO-90.

However, the present invention is not limited to pharmaceutical compositions containing drug substances having a relatively low solubility in water at a pH of between about 3.0 and 9.5 such as, e.g. between about 3.6 and 9. For structurants which fulfil a number of requirements, cf. below, the present inventor has found it possible also to obtain pharmaceutical compositions having suitable biopharmaceutical properties as well as a suitable storage stability, i.e. the compositions do not separate into at least two distinct phases within a well-defined period of time and under well-defined environmental conditions.

Thus, in another aspect, the invention relates to a pharmaceutical composition for administration of an active substance to a mammal, the composition comprising

i) a first substance, which is the active substance,

ii) a second substance which together with a liquid medium is capable of forming a liquid crystalline phase at room temperature, the liquid crystalline phase being selected from the group consisting of: a cubic, a hexagonal, a reverse hexagonal, a lamellar, a micellar and a reverse micellar liquid crystalline phase,

iii) a structurant

which - together with said second substance and water - at room temperature is capable of forming a liquid crystalline phase selected from the group consisting of: a cubic, a hexagonal, a reverse hexagonal, a lamellar, a micellar and a reverse micellar liquid crystalline phase,

which in itself together with water can form a liquid crystalline phase selected from the group consisting of: a cubic, a hexagonal, a reverse hexagonal and a lamellar, a micellar and a reverse liquid crystalline phase,

which - in a two component system wherein the structurant is one of the components and water is the other - is not capable of forming a cubic liquid crystalline phase at room temperature, and

which has a solubility in said second substance of at least 15% by weight at 60°C; and

iv) optionally, a liquid medium which is substantially homogeneously distributed in the composition,

the composition either being one in which the liquid crystalline phase has been generated by the second substance in combination with the structurant and together with a sufficient amount of the liquid medium originally present in the composition, or the composition being in a precursor form in which the second substance and the structurant have not generated the liquid crystalline phase, but are capable of forming the liquid crystalline phase <u>in situ</u> with moisture from the site at or to which the composition is administered, the moisture in this case constituting at least part of the liquid medium, and

the composition being substantially homogeneous and having such a physical stability that substantial no irreversible phase separation into two or more distinct phases can be observed visually after storage of the composition at 25°C and 60% relative humidity for one week.

The present inventor has also found that the content of the substance which is capable of generating a liquid crystalline phase (i.e. the substance denoted "second substance" which e.g. is a fatty acid ester) can be reduced by incorporating at least 5% by weight of certain pharmaceutically acceptable excipients and such a reduction of the content of e.g. fatty acid ester does not significantly deteriorate or negatively influence the biopharmaceutical properties of the composition. The effect of such pharmaceutically acceptable excipients is most likely a diluting effect of the content of the liquid crystalline phase present in the composition while no significant diluting effect is observed with respect to the biopharmaceutical properties of the composition (e.g. release properties, bioadhesion, storage stability).

Accordingly, in a still further aspect, the invention relates to a pharmaceutical composition for administration of an active substance to a mammal, the composition comprising

i) a first substance which is the active substance,

ii) a second substance which together with a liquid medium - at room temperature is capable of forming a liquid crystalline phase selected from the group consisting of: a cubic, a hexagonal, a reverse hexagonal, a lamellar, a micellar and a reverse micellar liquid crystalline phase,

iii) a pharmaceutically acceptable excipient in a concentration of at least 5% by weight based on the total composition, and

iv) optionally, a liquid medium which is substantially homogeneously distributed in the composition,

the composition either being one in which the liquid crystalline phase has been generated by the second substance together with a sufficient amount of the liquid medium originally present in the composition, or the composition being in a precursor form in which the second substance has not generated the liquid crystalline phase, but is capable of forming the liquid crystalline phase in situ with moisture from the site at or to which the composition is administered, the moisture in this case constituting at least part of the liquid medium,

the composition being substantially homogeneous and having such a physical stability that substantial no irreversible phase separation into two or more distinct phases can be observed visually after storage of the composition at 25°C and 60% relative humidity for one week,

the composition containing at the most about 60% by weight of said second substance.

As it appears from the aspects of the invention mentioned above, a liquid medium may optionally be present. In those case where a liquid medium is not present, the composition is in the form of a so-called "precursor composition", i.e. a composition in which a liquid crystalline phase has not been generated but which upon application to or on the mammal is capable of generating a liquid crystalline phase by means of moisture or body fluid present on the application site. The compositions of the invention may also be presented in precursor form even if a liquid medium is included in the composition. In such case, either the concentration of the liquid medium is too low to enable a formation of the liquid crystalline phase in the composition or the liquid medium is of a type with which the second substance does not form a liquid crystalline phase. In these cases, the liquid crystalline phase is formed in situ after application to the mammal by means of the moisture or body fluid present on the application site.

In general, the pharmaceutical compositions according to the invention are intended for administration to a mammal such as a human. The underlying formulation principle of compositions according to the invention is so generally applicable that composition suitable for almost any application site or administration route can be prepared by means of methods well known in the pharmaceutical practice. Preferably, the pharmaceutical compositions according to the invention are intended for application to or through undamaged or damaged skin or mucosa of an animal such as a human. The mucosa is preferably selected from oral, buccal, nasal, vaginal, rectal, aural, lung, and gastrointestinal mucosa. The skin or mucosa may also be inflamed. The composition may also be administered to body cavities such as the oral cavity or by the buccal route. Furthermore, the composition may be applied on or at a tooth or a dental pocket.

Furthermore, a pharmaceutical composition according to the invention may also be applied to a nail of an animal such as a human.

Liquid crystalline phase and suitable substances capable of forming liquid crystalline phases

As mentioned above an important property of a composition according to the present invention is its ability to generate a liquid crystalline phase. The term "liquid crystalline phase" as used herein is used to denote an intermediate state between solid crystals and isotropic liquids, characterized by long-range order and short-range properties close to those of a simple liquid or solution (Keller et al., Handbook of Liquid Crystals, Verlag Chemie, Weinheim, Germany, 1980).

The main component in a composition according to the invention - which is responsible for the formation of a liquid crystalline phase - is the so-called "second substance". As appears from the

above, another component in a composition according to aspects of the invention may also be capable of forming a liquid crystalline phase. Such a substance is in the present context denoted a "structurant". A structurant takes part in the liquid crystalline phase generated by the second substance, but need not be able to generate a liquid crystalline phase in compositions without any second substance present. Furthermore, a structurant may generate a quite different liquid crystalline phase than the second substance under the same conditions and in such a case, the present inventor has observed that the liquid crystalline phase generated by a composition of the invention is the one of the second substance. Although further experiments need to be carried out in order to confirm that this observation is a general one, it is at present contemplated that i) the second substance may be responsible for what kind of liquid crystalline phase a composition will generate or ii) the second substance may together with the structurant generate a liquid crystalline phase of a different kind than expected taken the nature of the second substance into account. Many of the classes of substances and examples of specific substances which are suitable for use as second substances may of course also be suitable for use as structurants (and vice versa) provided that the specific requirements claimed are fulfilled.

Examples of suitable substances with an excellent ability of forming a liquid crystalline phase are fatty acid esters like, e.g., glyceryl monoesters of fatty acids. Other substances which have ability of forming a liquid crystalline phase are found among amphiphilic substances such as polar lipids, surfactants and emulsifiers. Specific examples of glyceryl monoesters of fatty acids include glycerylmonooleate (monoolein) and glycerylmonolinoleate. Such fatty acid esters are capable of forming various crystalline phases upon contact with a hydrophilic medium such as water or glycerol. As will be explained in further detail below, these fatty acid esters also show so-called bioadhesive properties.

Liquid crystalline phases may be a cubic (three cubic liquid crystalline phases are well-characterised: i) the body-centred lattice, ii) the primitive diamond lattice, and iii) the gyroid), reverse cubic, hexagonal, reverse hexagonal, lamellar, micellar or reverse micellar phase. By the term "cubic liquid crystalline phase" herein is meant a thermodynamically stable, viscous and optically isotropic phase made of a suitable substance such as, e.g., a fatty acid ester and a liquid medium such as, e.g., an aqueous medium. The cubic liquid crystalline phase is contemplated to be build up of closed reversed micelles. The term "aqueous medium" includes media containing water or another hydrophilic and water-miscible substance such as, e.g., glycerol. The terms "hexagonal phase" and "reverse hexagonal phase", respectively, are used herein to describe thermodynamically stable, viscous and optically anisotropic phases characterized by long-range order in two dimensions and made of a suitable substance such as, e.g., a fatty acid ester and a liquid medium such as, e.g., an aqueous medium. The term "lamellar phase" is characterised by a long-range order in one dimension. The lamellar structure is the origin of liposomes having

spherical shells of lipid bilayers. The various liquid crystalline phases can be detected and identified by use of polarized light or by means of X-ray diffraction pattern analysis (see the Examples herein). The cubic liquid crystalline phase is normally the preferred phase in the compositions of the invention, but also, e.g., the reverse hexagonal and the reverse cubic liquid crystalline phase may be an interesting liquid crystalline phase in the compositions according to the invention, notably in compositions which are in precursor form.

In accordance with the above-mentioned observations, the so-called "second substance" for use in compositions according to the invention may be a fatty acid ester which is capable of forming a liquid crystalline phase on contact with a suitable liquid medium. The liquid of the liquid medium is suitably water, glycerol or an aqueous medium. An aqueous medium is a medium containing water at least in part.

Apart from aqueous solutions or dispersions, a medium with which the liquid crystalline phase is made may, especially for the precursor embodiment of the composition, at least in part be constituted by any body fluid or secretion which contains water and with which upon application the composition comes into contact, such as, e.g. in the case of a human body fluid, saliva, sweat, gastric juice, etc. As indicated above, the body fluid may induce formation of a liquid crystalline phase when a second substance such as a fatty acid ester is contacted with such a liquid.

However, in many embodiments, a composition according to the invention will be one in which the liquid crystalline phase is already present, that is, the liquid crystalline phase has already been established by interaction between a liquid medium present in the composition and the second substance such as a fatty acid ester. In such cases, the liquid of the liquid medium may typically be, e.g., water or glycerol or a mixture thereof, water often being a preferred liquid.

The fatty acid esters capable of generating a liquid crystalline phase as evidenced by one of the test methods described herein are fatty acid esters (i.e. composed of a fatty acid component and a hydroxy-containing component) wherein the fatty acid component of the fatty acid ester is a saturated or unsaturated fatty acid having a total number of carbon atoms of from C_6 to C_{26}.

Specific examples of saturated fatty acid moieties in the fatty acid esters according to the invention are selected from the group consisting of moieties of caproic acid, caprylic acid, capric acid, lauric acid, myristic acid, palmitic acid, stearic acid, arachidic acid, and behenic acid.

Specific examples of unsaturated fatty acid moieties in the fatty acid esters according to the invention are moieties selected from the group consisting of palmitoleic acid, oleic acid, linoleic acid, linolenic acid, and arachidonic acid.

Particularly suitable fatty acid esters for use in compositions according to the invention are fatty acid esters which are selected from the group consisting of fatty acid esters of polyhydric alcohols, fatty acid esters of hydroxycarboxylic acids, fatty acid esters of monosaccharides, fatty acid esters of glycerylphosphate derivatives, fatty acid esters of glycerylsulfate derivatives, and mixtures thereof. In those cases where the hydroxy-containing component of the fatty acid ester is polyvalent, the hydroxy-containing component may be partially or totally esterified with a fatty acid component or with mixtures of fatty acid components.

The polyhydric alcohol component of the fatty acid ester for use in compositions according to the invention is preferably selected from the group consisting of glycerol, 1,2-propanediol, 1,3-propanediol, diacylgalactosylglycerol, diacyldigalactosylglycerol, erythritol, xylitol, adonitol, arabitol, mannitol, and sorbitol. The fatty acid esters formed from such polyhydric alcohols may be mono- or polyvalent such as, e.g., divalent, trivalent, etc. In particular fatty acid monoesters have proved to have bioadhesive properties and are therefore preferred fatty acid esters for use in compositions according to the invention. The position of the polyvalent alcohol on which the ester bond(s) is(are) established may be any possible position. In those cases where the fatty acid ester is a diester, triester, etc. the fatty acid components of the fatty acid ester may be the same or different. In a most preferred aspect of the present invention, the polyhydric alcohol component is glycerol.

Examples of fatty acid esters for use in compositions according to the invention and wherein the hydroxy-containing component is a polyhydric alcohol are glycerylmonooleate, glycerylmonolinoleate, glycerol monolinoleate, and mixtures thereof. These fatty acid esters have especially promising bioadhesive properties, confer the Examples herein.

In those cases where the fatty acid ester for use in compositions according to the present invention is formed between a hydroxycarboxylic acid (or a derivative thereof) and a fatty acid (or a derivative thereof), the hydroxycarboxylic acid component of the fatty acid ester is preferably selected from the group consisting of malic acid, tartaric acid, citric acid, lactic acid, and sorbic acid. An interesting example of a fatty acid ester for use in compositions according to the invention is a fatty acid monoester of citric acid.

As mentioned above, the hydroxy-containing component of a fatty acid ester for use in compositions according to the present invention may also be a saccharide, such as a monosaccharide such as, e.g., glucose, mannose, fructose, threose, gulose, arabinose, ribose, erythrose, lyxose, galactose, sorbose, altrose, tallose, idose, rhamnose, or allose. In those cases where the hydroxy-containing component is a monosaccharide, the fatty acid ester is preferably

a fatty acid monoester of a monosaccharide selected from the group consisting of sorbose, galactose, ribose, and rhamnose.

The hydroxy-containing component of a fatty acid ester for use in compositions according to the invention may also be a glycerylphosphate derivative such as, e.g., a phospholipid selected from the group consisting of phosphatidic acid, phosphatidylserine, phosphatidylethanolamine, phosphatidylcholine, phosphatidylglycerol, phosphatidylinositole, and diphosphatidylglycerol.

Other interesting phospholipids are DEPE (1,2 dielaidoyl-sn-glycerol-3-phosphoethanolamine) and DMPE (PEG 550) (1,2-dimyristoyl-sn-glycero-3-phosphoethanolamine-N-(polyethylene glycol)550).

Especially interesting compounds having a phospholipid moiety are compounds wherein the fatty acid ester is a fatty acid ester of a glycerylphosphate derivative, and the fatty acid component is selected from the group consisting of lauric acid, myristic acid, palmitic acid, stearic acid, oleic acid, linoleic acid, linolenic acid, and behenic acid. Examples of such useful fatty acid esters are dioleyol phosphatidylcholine, dilauryl phosphatidylcholine, dimyristyl phosphatidylcholine, dipalmitoyl phosphatidylcholine, distearoyl phosphatidylcholine, dibehenoyl phosphatidylcholine, dimyristyl phosphatidylethanolamine, dipalmitoyl phosphatidylethanolamine, dioleyl phosphatidylglycerol, dilauryl phosphatidylglycerol, dimyristoyl phosphatidylglycerol, dipalmitoyl phosphatidylglycerol, distearoyl phosphatidylglycerol, dipalmitoyl phosphatic acid and mixtures thereof.

Most of the fatty acid esters for use in compositions according to the invention are well-known chemical compounds which are commercially available or may be prepared by means of conventional esterification procedures involving e.g. reaction of a fatty acid derivative such as, e.g., the corresponding acid chloride with a hydroxy-containing compound (if necessary protected with suitable protection groups) and subsequently isolating the fatty acid ester, if necessary after removal of any protecting group. Many of the commercially available fatty acid esters are employed in the food industry and in general, no steps are taken in order to obtain an approximately 100% pure fatty acid ester. As an example it can be mentioned that glycerylmonooleate from Danisco Ingredients A/S, Denmark is a very pure product containing about 98% w/w monoesters of which more than about 80% w/w (such as about 92% w/w) is glycerylmonooleate; the remaining monoesters are glycerylmonolinoleate, glyceryl monopalmitate and glyceryl monostearate. The fatty acid ester products for use in compositions according to the invention may thus be mixtures of fatty acid esters.

Examples of fatty acid esters with excellent bioadhesive properties as well as an excellent ability of forming a liquid crystalline phase are glyceryl monoesters of fatty acids. Specific examples include glycerylmonooleate (monoolein) and glycerylmonolinoleate. As mentioned above, such fatty acid esters are capable of forming various crystalline phases upon contact with a hydrophilic medium such as water or glycerol, a preferred liquid crystalline phase being the cubic liquid crystalline phase.

Thus, very interesting compositions according to the invention are compositions in which the fatty acid ester is glycerylmonooleate or glycerylmonolinoleate, in particular glycerylmonooleate.

It has been found that the stability of the composition is considerably enhanced, such as resulting in a storage stability of at least 2 years at 25°C, when the glycerylmonooleate product (as is well known, fatty acid esters are almost invariably mixed products) contained in the product fulfils certain purity standards. Thus, the glycerolmonooleate product used for the preparation of the composition should contain at the most 4% of saturated monoglyceride and should preferably contain at least 88% of glycerylmonooleate, more preferably at least 89%, such as at least 90% or at least 91%, in particular at least 92%, of glycerylmonooleate.

When the composition is a precursor type composition, the liquid medium is either not present at all or is present in small amounts, such as an amount of at least 0.5% by weight, such as at least 1% by weight, calculated on the total composition, e.g. at least 2% by weight, calculated on the total composition, or up to at least 5% or in certain cases at least 10%, calculated on the total composition.

In non-precursor compositions, the liquid medium is normally present in an amount of at least 20% by weight, calculated on the total composition, such as at least 25% or at least 30% by weight, calculated on the total composition, and a preferred amount is often in the range of 25-50% such as 25-40% by weight, in particular 25-35%, 27-40%, 27-35% or 30-40% by weight, calculated on the total composition.

Normally, the concentration of the second substance in a composition according to the invention is at least about 10% by weight such as, e.g., at least 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, or 70% by weight calculated on the composition.

In other terms, the concentration of the second substance in the composition is in a range corresponding to from about 10% to about 90% such as, e.g. about 15%-85%, about 20%-80%, about 25%-75%, about 25%-70%, about 25%-65%, about 25%-60%, about 25%-55%, about 30%-

50%, about 35%-55%, about 30%-45% or about 30%-40% by weight based on the total composition.

Generally, the maximal concentration of the second substance in the composition is at the most about 60% such as, e.g. at the most about 55%, about 50%, about 45%, about 40%, about 35%, about 30%, about 25% or about 20% by weight based on the total composition.

Structurants

As indicated above the gist of the present invention relates to the use of certain substances as substitutes for at least a part of the substance (e.g. a fatty acid ester) which is capable of forming a liquid crystalline phase. Surprisingly, the inventor has found that when, e.g., the fatty acid ester component is substituted by so-called structurants then the lattice structure of the liquid crystalline phase formed in the composition (or <u>in situ</u> if the composition is a precursor composition) is not only based on the fatty acid ester itself but the structurant takes part in this lattice. Thus, the structurant imparts the lattice structure to the composition and, thus, the content of lattice structure in the composition is of the same order of magnitude as if no substitution has taken place. When adding active substances or additives to a composition which is capable of forming a liquid crystalline phase, the general observation is that the active substance or additive is enclosed or enveloped in the composition without participating in the formation of the lattice structure. In general, such substances can only be present in the composition to a certain extent beyond which the substance will exert a negative influence on the formation of a liquid crystalline phase resulting in that either no liquid crystalline phase is formed or the biopharmaceutical properties of the composition are negatively influenced. In general, substances can be incorporated in a concentration of at the most about 10% by weight without any significant change in the ability of the composition to form a liquid crystalline phase or to undergo a phase transition.

As mentioned above a structurant participates in the liquid crystalline structure preferably formed together with a fatty acid ester. A suitable structurant is typically an amphiphilic substance having a molecular weight of at the most 2000 or an emulsifier or a surfactant. Tensides (anionic, cationic, non-ionic like e.g. sorbitan esters, sorbitan macrogol esters (polysorbates)), polar lipids, glycolipids, lechitins, palmitoyl muramic acid (PMA), substances having surface active properties like e.g. certain cellulose derivatives, sorbitan oleate, sorbitan laurate, lanolin and derivatives thereof and ethoxylated derivatives of lanolin (Aqualose W20, Aqualose L30 and Aqualose L75) are also examples of suitable structurants for use in compositions according to the invention.

Sorbitan esters are a series of mixtures of partial esters of sorbitol and its mono- and di-anhydrides with fatty acids. Examples of suitable sorbitan esters for use as structurants in a composition according to the invention are:

Sorbitan di-isostearate
Sorbitan dioleate
Sorbitan monoisostearate
Sorbitan monolaurate
Sorbitan monooleate
Sorbitan monopalmitate
Sorbitan monostearate
Sorbitan sesqui-isostearate
Sorbitan sesquioleate
Sorbitan trioleate
Sorbitan sesquistearate
Sorbitan tri-isostearate
Sorbitan tristearate
Sorbitan tristearate

Polyoxyethylene sorbitan fatty acid esters (polysorbates) are a series of fatty acid esters or sorbitol and its anhydrides copolymerized with approximately 20 moles of ethylene oxide for each mole of sorbitol and its anhydrides. Examples of suitable polysorbates for use in the present context are:

Polysorbate 20
Polysorbate 21
Polysorbate 40
Polysorbate 60
Polysorbate 61
Polysorbate 65
Polysorbate 80
Polysorbate 81
Polysorbate 85
Polysorbate 120

If a liquid medium such as, e.g., water is present in a composition, the polysorbates may be dissolved or dispersed therein.

In order to be able to participate in the lattice structure of the liquid crystalline phase, it is contemplated that a structurant should possess a hydrophilic as well as hydrophobic portion. A useful structurant normally have the following molecular characteristics:

Chains:
alkyl chains (saturated or unsaturated), polyethylene chains and/or polyoxyethylene chains

and contain at least one of the following functional groups (or a radical thereof):

sugar, oxyethylene, glycerol, hydroxy, polyhydroxy, amino acid, sulfates, and/or phosphates.

Suitable structurants are also found among the substances which normally are denoted emulsifiers. Preferably, the structurant has a saturated or unsaturated, branched or unbranched, substituted or unsubstituted C_6-C_{26}-alkyl chain, and/or the structurant is a compound which contains a polyethylene group.

Furthermore, an important property of a structurant which is suitable for use in compositions according to the present invention is its solubility in the second substance such as e.g. a fatty acid ester or mixtures of fatty acid esters. It is believed that the two components (i.e. the second substance and the structurant) should be miscible (or compatible) and "like each other" in order to be able to cooperate when the lattice structure is formed. Thus, the solubility of the structurants in the second substance like e.g. a fatty acid ester or mixtures of fatty acid esters should preferably be at least about 15%, such as at least about 20% or about 25% by weight at 60°C.

In certain interesting embodiments of the invention the structurant is a substance which - together with the second substance like a fatty acid ester and a liquid medium - is capable of forming a cubic liquid crystalline phase.

It is contemplated that the preferred structurants are substances which - in a two component system of the structurant as a first component and water as a second component - are capable of forming a non-cubic liquid crystalline phase.

However, a requirement for the structurant is not that it is capable of forming the same liquid crystalline phase at room temperature as the second substance. In particular, most surprising the inventor has found that a substance like Vitamin E TPGS - which is a very important structurant in this context and which in itself together with water is not capable of forming a

cubic liquid crystalline phase at room temperature - together with fatty acid esters (as second substances) and water forms a cubic liquid crystalline phase.
Therefore, interesting examples of structurants are substances which - in a two component system of the structurant and water - do not form a cubic liquid crystalline phase at a temperature of between 20-40°C.

A composition according to the invention may of course also comprise more than one structurant such as, e.g., a combination of two or more structurants.

With respect to the concentration of the structurant(s) in the composition it is preferred that the concentration (of the structurants taken either alone or in combination) is at least 1% by weight such as, e.g., at least 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, or 55% by weight based on the total weight of the composition.

The concentration range is typically in a range of from about 1% to about 60% such as, e.g., from about 5% to about 55%, from about 5% to about 50%, from about 5% to about 45%, from about 7.5% to about 40%, or from about 10% to about 35% by weight based on the total weight of the composition.

Normally, the maximal concentration of a structurant in the composition is at the most about 45% by weight such as, e.g., at the most least about 40% or about 35% by weight based on the total weight of the composition.

Normally, compositions comprising e.g. glyceryl monooleate (GMO)/water without any content of a structurant must have a concentration of the GMO of at least 60-65% by weight in order to have a certain suitable and acceptable storage stability and/or to avoid an excess of water present in the composition. However, the present inventor has found that when e.g. GMO is substituted by a structurant, compositions having a concentration of e.g. GMO below and well below 60% by weight have shown to be stable for at least one week at room temperature and 60% relative humidity. In the present context the stability of the composition is the physical stability, i.e. stability with respect to phase separation (i.e. not necessarily change in liquid crystalline phase) into two or more distinct phase. The phase separation must be irreversible, i.e. no reestablishment of a homogeneous composition can be observed visually by shaking the composition at room temperature for 2 days and the distinct phases formed by either be liquid, semi-solid or solid phases. In some cases, a physical instability of the composition may be due to a change in the liquid crystalline phase present in the composition. Such a change in the liquid crystalline phase may either be due to i) a chemical change of either the second substance or the structurant, ii) a negative influence on the liquid crystalline phase by any component included in

the composition, or iii) the fact that the concentration of the constituents of the composition is near a point in the phase diagram where the liquid crystalline phase changes from one phase to another or is destroyed (i.e. the concentration is near the borderline of the stable area of the liquid crystallin phase). In general, a composition according to the invention is substantially homogeneous and has such a physical stability that substantial no irreversible phase separation into two or more distinct phases can be observed visually after storage of the composition at 25°C and 60% relative humidity for one week or at least for one week such as, e.g., at least two weeks, 1 month, 1 year or preferably at least 2 years at 25°C.

The total concentration of the substances - which together with each other and an liquid medium such as, e.g., water are capable of generating a liquid crystalline phase - in a composition according the invention is typically at least about 50% by weight based on the weight of the total composition. Thus, in general the total concentration of the second substance such as, e.g., a fatty acid ester or mixture of fatty acid esters and the structurant(s) is at least 50% by weight based on the total composition.

Interesting embodiments of the invention are compositions wherein the liquid crystalline phase has been generated by a liquid medium present in the composition and wherein the total concentration of the second substance like e.g. a fatty acid ester or mixture of fatty acid esters and the structurant(s) is at least 50% such as at least 55%, 60%, 65%, 70% or 75% by weight based on the total composition.

As mentioned above, a composition according to the invention may also be in a precursor form. Examples of interesting compositions are those wherein the total concentration of the fatty acid ester or mixture of fatty acid esters and the structurant(s) is at least 50% such as at least 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or 99.5% by weight based on the total composition.

Specific examples of a suitable structurant for use in a composition according to the invention are, e.g., a phospholipid selected from the group consisting of phosphatidic acid, phosphatidylserine, phosphatidylethanolamine, phosphatidylcholine, phosphatidylglycerol, phosphatidylinositol, and diphosphatidylglycerol.

Other interesting phospholipids are DEPE (1,2 dielaidoyl-sn-glycerol-3-phosphoethanolamine) and DMPE (PEG 550) (1,2-dimyristoyl-sn-glycero-3-phosphoethanolamine-N-(polyethylene glycol)550).

More specifically, the structurant may be a fatty acid ester of a glycerylphosphate derivative or a glycerylsulfate derivative, and the fatty acid component is selected from the group consisting of

lauric acid, myristic acid, palmitic acid, stearic acid, oleic acid, linoleic acid, linolenic acid, and behenic acid. Specific examples include structurants wherein the fatty acid ester is selected from the group consisting of dioleyol phosphatidylcholine, dilauryl phosphatidylcholine, dimyristyl phosphatidylcholine, dipalmitoyl phosphatidylcholine, distearoyl phosphatidylcholine, dibehenoyl phosphatidylcholine, dimyristyl phosphatidylethanolamine, dipalmitoyl phosphatidylethanolamine, dioleyl phosphatidylglycerol, dilauryl phosphatidylglycerol, dimyristoyl phosphatidylglycerol, dipalmitoyl phosphatidylglycerol, distearoyl phosphatidylglycerol, dipalmitoyl phosphatic acid and mixtures thereof.

A presently preferred type of structurant is phosphatidylcholine such as, e.g., a phosphatidylcholine containing product like Epikuron 200, Epikuron 145, Lipoid S75 or Lipoid S100.

In a composition according the invention wherein the structurant is a phosphatidylcholine or a derivative or analog thereof, the concentration of the structurant is preferably in a range of from about 1 to about 75% such as, e.g., from about 5 to about 55%, from about 5% to about 35% or from about 10 to about 20% by weight based on the total weight of the composition.

Another group of substances which are suitable structurants for use in a composition according to the invention is tocopherols. In the present context the term "tocopherols" is used to broadly include all Vitamin E or Vitamin E-like substances, derivatives and analogs thereof. The term includes all tocol and tocotrienol derivatives such as e.g. methyl tocol. More specifically, in the present context, a tocopherol is selected from the group consisting of β-tocopherols, sorbitan esters of tocopherols, d-α-tocopherol, d,l-α-tocopherol, d-α-tocopherol acetate, d,l-α-tocopherol acetate, d-α-tocopherol succinate, d,l-α-tocopherol succinate, d-α-tocopherol nicotinate, d,l-α-tocopherol nicotinate, tocopherylpolyethylene glycol succinate such as d-α-tocopherylpolyethylene glycol succinate or d,l-α-tocopherylpolyethylene glycol succinate, and derivatives such as fatty acid ester derivatives and analogues thereof.

The tocopherylpolyethylene glycol succinate is selected from the group consisting of:
d-α-tocopherylpolyethylene glycol 200 succinate,
d,l-α-tocopherylpolyethylene glycol 200 succinate,
d-α-tocopherylpolyethylene glycol 300 succinate,
d,l-α-tocopherylpolyethylene glycol 300 succinate,
d-α-tocopherylpolyethylene glycol 400 succinate,
d,l-α-tocopherylpolyethylene glycol 400 succinate,
d-α-tocopherylpolyethylene glycol 500 succinate,
d,l-α-tocopherylpolyethylene glycol 500 succinate,

d-α-tocopherylpolyethylene glycol 600 succinate,
d,l-α-tocopherylpolyethylene glycol 600 succinate,
d-α-tocopherylpolyethylene glycol 700 succinate,
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d-α-tocopherylpolyethylene glycol 900 succinate,
d,l-α-tocopherylpolyethylene glycol 900 succinate,
d-α-tocopherylpolyethylene glycol 1000 succinate,
d,l-α-tocopherylpolyethylene glycol 1000 succinate,
d-α-tocopherylpolyethylene glycol 1100 succinate,
d,l-α-tocopherylpolyethylene glycol 1100 succinate,
d-α-tocopherylpolyethylene glycol 1200 succinate,
d,l-α-tocopherylpolyethylene glycol 1200 succinate,
d-α-tocopherylpolyethylene glycol 1300 succinate,
d,l-α-tocopherylpolyethylene glycol 1300 succinate,
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d,l-α-tocopherylpolyethylene glycol 1400 succinate,
d-α-tocopherylpolyethylene glycol 1450 succinate,
d,l-α-tocopherylpolyethylene glycol 1450 succinate,
d-α-tocopherylpolyethylene glycol 1500 succinate,
d,l-α-tocopherylpolyethylene glycol 1500 succinate,
d-α-tocopherylpolyethylene glycol 1600 succinate,
d,l-α-tocopherylpolyethylene glycol 1600 succinate,
d-α-tocopherylpolyethylene glycol 1700 succinate and
d,l-α-tocopherylpolyethylene glycol 1700 succinate.

Preferred tocopherols for use in a composition according to the present invention are d-α-tocopherylpolyethylene glycol 1000 succinate (in the following denoted vitamin E TPGS or simply TPGS) or d,l-α-tocopherylpolyethylene glycol 1000 succinate.

A composition according to the invention containing a tocopherol as a structurant has typically a concentration of the tocopherol of at the most about 30% such as at the most about 25%, 20%, 15%, 10%, 5%, 2.5% or 1% by weight based on the total weight of the composition.

Presently preferred compositions according to the invention are those wherein the structurant is a combination of vitamin E TPGS and a phosphatidylcholine containing product such as, e.g., Epikuron 200. In such compositions the concentration of vitamin E TPGS is generally in a range corresponding to from about 1% to about 30% such as, e.g., from about 5% to about 25%, from about 5% to about 20% or from about 10% to about 20% by weight and the concentration of Epikuron 200 is in a range corresponding to from about 2.5% to about 40% such as, e.g., about 5% to about 25% or from about 10% to about 20% by weight based on the total composition.

Pharmaceutically acceptable excipients for use in a composition according to the invention

As mentioned above, an aspect of the invention relates to compositions wherein at least a part of the substance which together with a liquid medium such as, e.g., water is capable of forming a liquid crystalline phase at room temperature can be substituted by certain pharmaceutically acceptable excipients. As mentioned in the introduction addition of a pharmaceutically acceptable excipient to a composition containing a liquid crystalline phase or a precursor composition will normally lead to a disruption in the liquid crystalline phase. Therefore, such substance is generally only added in very small concentrations such as, e.g., about 1-5% by weight based on the total composition. The present inventor has surprisingly found that certain pharmaceutically acceptable excipients may be added in much larger concentrations without having any substantially negative influence on the biopharmaceutical properties of the composition. Thus, the concentration of such excipients may be at least about 5% by weight such as, e.g, at least about 8%, 9%, 10%, 15% or 20% by weight.

Suitable pharmaceutically acceptable excipients may either i) be soluble in the second substance or in the liquid crystalline phase, i.e. having a solubility of more than about than about 15% such as more than about 25%, 30% or 50% by weight in the second substance (or liquid crystalline phase) at 60°C, or ii) have a relative low solubility in the second substance such as, e.g., a solubility of less than 15% such as less than about 12.5%, 10%, 7.5%, 5% or 1% by weight in the second substance at 60°C. More specifically, the pharmaceutically acceptable excipient may have a solubility of less than about 15% such as less than about 10%, about 5%, about 2.5%, about 1%, or about 0.5% by weight in the liquid crystalline phase at room temperature.

Examples of suitable pharmaceutically acceptable excipients are found e.g. among inert diluents or fillers selected from the group consisting of sucrose, sorbitol, sugar, mannitol, microcrystalline cellulose, carboxymethylcellulose sodium, methylcellulose, hydroxypropyl methylcellulose, ethylcellulose, starches including potato starch, calcium carbonate, sodium chloride, lactose, calcium phosphate, calcium sulfate, sodium phosphate, and a polysaccharide such as, e.g.,

carmelose, a chitosan, a pectin, xanthan gum, a carrageenan, locust bean gum, acacia gum, a gelatin, an alginate, and dextrans and salts thereof.

Preferably, a in composition according to the above-mentioned aspect of the invention the concentration of the second substance in the composition is at the most about 60% such as, e.g., at the most about 55%, 50%, 45%, 40%, 35%, 30%, 25%, 20%, 15%, or 10% by weight based on the total composition.

Examples of suitable pharmaceutically excipients which are soluble in the second substance or in the liquid crystalline phase are e.g. sorbitan esters such as, e.g., polysorbates; and macrogols. In the present context, solvents like e.g., water, glycerol, alcohols like e.g. ethanol and isopropylalcohol are examples of a liquid medium and are not intended to be examples of soluble pharmaceutically acceptable excipients.

Liquid medium

As mentioned above a composition according to the invention may optionally comprise a liquid medium. A liquid medium may be present in compositions in which a liquid crystalline phase between the second substance and the liquid medium has been generated as well as in the so-called precursor compositions in which the liquid crystalline phase has not been generated in the composition but is to be formed upon administration of the composition to a mammal. In the latter case, any liquid medium present in the precursor composition may or may not take part in the formation of a liquid crystalline phase together with any moisture from the application site or body fluid present at or on the application site.

In general, a liquid medium is present in a concentration of at least about 0.5% by weight, such as at least about 1%, at least about 2%, at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25% or at least about 30% by weight, calculated on the total composition.

In non-precursor compositions, a liquid medium normally is present in a concentration of 20%-50% such as, e.g., about 25%-35% about 25%-30% or about 30%-40% by weight, calculated on the total composition.

In preferred non-precursor compositions, a liquid medium is present in a concentration of 25%-40% such as, e.g, about 25-35%, about 30%-40% or 27%-37% by weight, calculated on the total composition.

Generally preferred liquid media which participate in the formation of a liquid crystalline phase are water, glycerol, alcohols like e.g. ethanol and mixtures thereof.

Active substances

In the present context the term "active substance" is intended to mean any biologically or pharmacologically active substance or antigen-comprising material; the term includes drug substances which have utility in the treatment or prevention of diseases or disorders affecting animals or humans, or in the regulation of any animal or human physiological condition and it also includes any biologically active compound or composition which, when administered in an effective amount, has an effect on living cells or organisms.

Examples of active substances of particular importance with respect to all aspects of the invention are the so-called antiherpes virus agents which have been or are developed for the treatment of herpes virus infections [herpes simplex virus types 1 and 2 (HSV-1 and HSV-2), varicella zoster virus (VZV), cytomegalovirus (CMV), Epstein-Barr virus (EBV)]. The antiherpes virus agents include antiviral drugs and prodrugs thereof, such as nucleosides, nucleoside analogues, phosphorylated nucleosides (nucleotides), nucleotide analogues and salts, complexes and prodrugs thereof; e.g. guanosine analogues, deoxyguanosine analogues, guanine, guanine analogues, thymidine analogues, uracil analogues and adenine analogues. Especially interesting antiherpes virus agent for use either alone or in combination in a composition according to the present invention are selected from acyclovir, famciclovir, deciclovir, penciclovir, zidovudin, ganciclovir, didanosin, zalcitabin, valaciclovir, sorivudine, lobucavir, brivudine, cidofovir, n-docosanol, ISIS-2922, and prodrugs and analogues thereof. Details concerning active substances suitable for use in connection with the present invention as well as a description of other interesting active substances are given below.

As mentioned above, an important example of an active substance is an antiviral drug, such as a nucleoside or a nucleoside analogue, e.g. selected from acyclovir, famciclovir, deciclovir, penciclovir, zidovudin, ganciclovir, didanosin, zalcitabin, valaciclovir, sorivudine, lobucavir, brivudine, cidofovir, n-docosanol, ISIS-2922 and salts and prodrugs thereof. However, also a large number of other drugs which in themselves have a low solubility as defined herein or the salts, esters, prodrugs or precursors of which have a low solubility are important active substances in the compositions of the invention. Furthermore, there is also a large number of drugs which advantageously can be incorporated in a composition according to the invention, either as the sole active substance (provided the solubility criteria are fulfilled) or in combination with another active substances. In the following is listed a number of active substances which either alone or in combination may be incorporated in a composition according to the present

invention. In particular a combination of an antiherpes virus agent and a glucocorticosteroid is of importance.

Examples of drugs which are of particular importance in connection with application to skin or mucosal surfaces are:

Acyclovir, famciclovir, ribavirin, zidovudin, ganciclovir, didanosin, zalcitabin, valaciclovir

amantadin, rimantadin

foskarnet

idoxuridin
fluoruracil

interferons and variants thereof, including alpha interferon, beta interferon, and gamma interferon,

tromantadin

lentinan
levofloxacin
stavudine
tacrine
vesnarinone
ampligen

atevirdine
delavirdine
hydroxyurea
indinavir sulfate
interleukin-2 fusion toxin, seragen
lamivudine
lidakol
nevirapine
onconase
saquinavir
topotecan

verteporfin
viraplex

CMV immunoglobulin
efalith
epervudine
podophyllotoxin
proxigermanium
rifabutin
bromovinyldeoxyuridine
ukrain
cidofovir
imiquimod
lamivudine
sorivudine
viraplex
afovirsen
amonafide
hypericin

provir
temoporfin
aphidicolin glycinate
ibobucavir
virend

AL-721
ampligen
arildone
brivudine
CD4
2-deoxy-D-glucose
desciclovir
dichloroflavan
didanosine
ditiocarb Sodium
edoxudine
enviroxime

fiacitabine
inosine Pranobex
peptide T
stavudine
tribavirin
trifluridine
vidarabine
zalcitabine

miconazol
fucidin
erythromycin
macrolides
NSAID's
peptides
insulin
polymycin
myperizin
antibiotics
nicotine
sucralfate
sucrose octasulfate
salicylic acid
urea
benzoylperoxide
minoxidil
heparinoid
methotrexate
ciclosporin

A listing of substances of potential interest comprises substances of the following groups:

sodium fluoride

anti-inflammatory drugs such as, e.g., ibuprofen, indomethacin, naproxen, diclofenac, tolfenamic acid, piroxicam, and the like;

narcotic antagonists such as, e.g., naloxone, nalorphine, and the like;

antiparkinsonism agents such as, e.g., bromocriptine, biperidin, benzhexol, benztropine, and the like;

antidepressants such as, e.g., imipramine, nortriptyline, pritiptylene, and the like;

antibiotic agents such as, e.g., clindamycin, erythromycin, fusidic acid, gentamicin, mupirocien, amfomycin, neomycin, metronidazole, silver sulphadiazine, sulphamethizole, bacitracin, framycetin, polymycin B, acitromycin, and the like;

antifungal agents such as, e.g., miconazol, ketoconazole, clotrimazole, amphotericin B, nystatin, mepyramin, econazol, fluconazol, flucytocine, griseofulvin, bifonazole, amorolfine, mycostatin, itraconazole, terbenafine, terconazole, tolnaftate, and the like;

antimicrobial agents such as, e.g., metronidazole, tetracyclines, oxytetracycline, and the like;

antiemetics such as, e.g., metoclopramide, droperidol, haloperidol, promethazine, and the like;

antihistamines such as, e.g., chlorpheniramine, terfenadine, triprolidine, and the like;

antimigraine agents such as, e.g., dihydroergotamine, ergotamine, pizotyline, and the like;

coronary, cerebral or peripheral vasodilators such as, e.g., nifedipine, diltiazem, and the like;

antianginals such as, e.g., glyceryl nitrate, isosorbide denitrate, molsidomine, verapamil, and the like;

calcium channel blockers such as, e.g., verapamil, nifedipine, diltiazem, nicardipine, and the like;

hormonal agents such as, e.g., estradiol, estron, estriol, polyestradiol, polyestriol, dienestrol, diethylstilbestrol, progesterone, dihydroergosterone, cyproterone, danazol, testosterone, and the like;

contraceptive agents such as, e.g., ethynyl estradiol, lynestrenol, etynodiol, norethisterone, mestranol, norgestrel, levonorgestrel, desogestrel, medroxyprogesterone, and the like;

antithrombotic agents such as, e.g., heparin, warfarin, and the like;

diuretics such as, e.g., hydrochlorothiazide, flunarizine, minoxidil, and the like;

antihypertensive agents such as, e.g., propanolol, metoprolol, clonidine, pindolol, and the like;

corticosteroids such as, e.g., beclomethasone, betamethasone, betamethasone-17-valerate, betamethasone-dipropionate, clobetasol, clobetasol-17-butyrate, clobetasol-propionate, desonide, desoxymethasone, dexamethasone, diflucortolone, flumethasone, flumethasone-pivalate, fluocinolone acetonide, fluocinonide, hydrocortisone, hydrocortisone-17-butyrate, hydrocortisone-buteprate, methylprednisolone, triamcinolone acetonide, budesonide, halcinonide, fluprednide acetate, alklometasone-dipropionate, fluocortolone, fluticason-propionate, mometasone-furate, desoxymethasone, diflurason-diacetate, halquinol, cliochinol, chlorchinaldol, fluocinolone-acetonid, and the like;

dermatological agents such as, e.g., nitrofurantoin, dithranol, clioquinol, hydroxyquinoline, isotretionin, methoxsalen, methotrexate, tretionin, trioxsalen, salicylic acid, penicillamine, and the like;

steroids such as, e.g., estradiol, progesterone, norethindrone, levonorgestrol, ethynodiol, levenorgestrel, norgestimate, gestanin, desogestrel, 3-keton-desogestrel, demegestone, promethoestrol, testosterone, spironolactone, and esters thereof,

nitro compounds such as, e.g., amyl nitrates, nitroglycerine and isosorbide nitrates,

opioid compounds such as, e.g., morphine and morphine-like drugs such as buprenorphine, oxymorphone, hydromorphone, levorphanol, fentanyl and fentanyl derivatives and analogues,

prostaglandins such as, e.g., a member of the PGA, PGB, PGE, or PGF series such as, e.g., misoprostol, dinoproston, carboprost or enaprostil,

a benzamide such as, e.g., metoclopramide, scopolamine,

a peptide such as, e.g., growth hormone releasing factors, growth factors (epidermal growth factor (EGF), nerve growth factor (NGF), TGF, PDGF, insulin growth factor (IGF), fibroblast growth factor (aFGF, bFGF, etc.), and the like), somatostatin, calcitonin, insulin, vasopressin, interferons, IL-2, urokinase, serratiopeptidase, superoxide dismutase (SOD), thyrotropin releasing hormone (TRH), luteinizing hormone releasing hormone (LH-RH), corticotrophin releasing hormone (CRF), growth hormone releasing hormone (GHRH), oxytocin, erythropoietin (EPO), colony stimulating factor (CSF), and the like,

a xanthine such as, e.g., caffeine, theophylline,

a catecholamine such as, e.g., ephedrine, salbutamol, terbutaline,

a dihydropyridine such as, e.g., nifedipine,

a thiazide such as, e.g., hydrochlorotiazide, flunarizine,

others such as, e.g., propanthelin, silver nitrate, enzymes like Streptokinases, Streptodases, vitamins like vitamin A, tretionin, isotretionin, acitretin, vitamin D, calcipotriol, interferon-α-2b, selen disulfide, pyrethione.

It will be understood that the compositions of the invention may also comprise combinations of active substances, e.g. an active substance together with a potentiator therefor.

It will of course also be understood that in the aspects of the invention wherein there is no specific requirement to the active substance, e.g. with respect to solubility, any substance which has a therapeutic or prophylactic activity may be incorporated in the composition.

Solubility of the active substance in the liquid crystalline phase

As mentioned above, in an aspect of the invention and in some embodiments of other aspects of the invention, the active substance of the composition of the invention is a substance which has a low solubility in the liquid crystalline phase such as, e.g., at the most about 20 mg/g at 20°C, at the most 15 mg/g at 20°C, e.g. at the most 10 mg/g at 20°C or lower, such as at the most 7 mg/g, 6.5 mg/g, 6 mg/g, 5..5 mg/g, 5 mg/g at 20°C. e.g. at the most 4 mg/g at 20°C or even at the most 3 mg/g or 2 mg/g or 1 mg/g at 20°C.

The determination of the solubility of the active substance in the liquid crystalline phase of the composition is, of course, performed on the liquid crystalline phase as formed. In practice, this means that when the composition is one in which the liquid crystalline phase has already been formed when the composition is applied, the determination of the solubility is performed on the composition itself. The determination of the solubility is suitably performed by microscopy to observe any crystals of the active substance. The determination of the concentration at which crystals are observed is performed after a period of at least one week after preparation of the composition or the liquid crystalline phase, or when equilibrium has been established. Normally, a series of tests with varying concentrations is performed to determine the concentration above which crystals are found. On the other hand, when the composition is a precursor composition, the liquid crystalline phase used as a reference in the solubility determination is a liquid crystalline phase imitating the liquid crystalline phase which will be formed when the

composition absorbs liquid from the site of application. This reference liquid crystalline phase is made up with water (as representing the liquid absorbed) in such an amount that the reference liquid crystalline phase is the same type of liquid crystalline phase as is generated from the precursor composition.

While the lower limit of the amount of the second substance such as, e.g., a fatty acid ester in the composition is determined by the requirement that the second substance, in the amount in question, must be able to form and maintain the liquid crystalline phase, the composition will in most cases contain at least 10% by weight, calculated on the composition, of the fatty acid ester, such as at least about 15%, 20%, 25%, 30%, or 35% by weight, and in some cases at least 40%, 45%, 50%, 55%, 60%, 65%, or 70% by weight, calculated on the composition, of the second substance. These numbers apply to the liquid crystalline phase present in the composition; in precursor compositions, the concentrations will, of course, be higher.

The pH of the liquid crystalline phase of the composition is in the range of 3.0-9.5 such as, e.g., 3.2-9.3, 3.4-9.1 or 3.6-9. At lower pH values, the composition may be irritating to the skin or mucosa on which it is applied; at higher pH values, the composition may be irritating and may also directly be etching. The pH of the liquid crystalline phase is determined by a method involving dispersing e.g. 10% of the liquid crystalline phase (containing the active substance and any excipients) in distilled water and measuring the pH in the water phase, equilibration between the liquid crystalline phase and a water phase and measuring the pH of the water phase at 20°C (e.g. using a rotomat for 2 hours). Alternatively, the pH of the liquid crystalline phase may be measured by means of an suitable pH electrode (see the Examples).

It is generally preferred that the upper limit of the pH of the liquid crystalline phase is 8. It is also preferred that the lower limit of the pH is 3.0 or higher, and thus, interesting pH ranges for the liquid crystalline phase are pH 3.0-8, such as, e.g., 3.1-8, 3.2-8, 3.3-8, 3.4-8, 3.5-8, 3.6-8, 3.7-8, 3.8-8, 3.9-8, 4.0-8, 4.1-8, 4.2-8, 4.3-8, 4.5-8, 4.75-8, or 5.0-8.

Furthermore, in an aspect of the invention and in embodiments of other aspects of the invention, the solubility of the active substance in water is very low, at the most 10 mg/g at 20°C and at a pH substantially identical to the pH of the liquid crystalline phase, determined as described herein. While a pH range is stated above for the liquid crystalline phase, it will be understood that by the water solubility of the active substance is meant the water solubility at the relevant pH, which is a pH substantially identical to the pH which will prevail in the composition, in other words, the pH of the liquid crystalline phase, this pH being determined as described herein. When the pH of the liquid crystalline phase, determined as described herein, is different from the pH which will result simply by dissolution of the active substance in water,

the water is adjusted to substantially the pH of the liquid crystalline phase by using a suitable buffer system when determining the solubility of the active substance. This buffer system should of course be so selected that, apart from the pH adjustment, it has substantially no influence on the solubility of the active substance in the buffered water.

The composition according to the present invention is very valuable in that it can provide a high release of active substances of very low water solubility, such as
a solubility of at the most 7 mg/g, such as at the most 5 mg/g at 20°C and at a pH substantially identical to the pH of the liquid crystalline phase, determined as described herein.

Of particular interest is also the fact that excellent release rates can be obtained of active substance whose solubility in water is at the most 3 mg/g or even at the most 2 mg/g at 20°C and at a pH substantially identical to the pH of the liquid crystalline phase, determined as described herein.

Alternatively, the active substance has an minimum aqueous solubility of at the most 10 mg/ml such as, e.g., 7 mg/ml, 5 mg/ml, 3 mg/ml and 1 mg/ml at 20°C and at a pH in a range corresponding to 3.0-9.5 such as, e.g. having a pH between 3.2 and 9.3, between 3.4 and 9.1 or between 3.6 and 9.0. The determination of the minimum aqueous solubility is performed by use of suitable buffers which are capable of maintaining the pH at the desired value and measures are taken to ensure that equilibrium is obtained between the undissolved and dissolved active substance, i.e. by employment of ultrasonic treatment and/or stirring for a well-defined time period. It will be appreciated that the pH-ranges and the aqueous solubility values given above when the aqueous solubility is determined at a pH corresponding to the pH prevailing in the liquid crystalline phase apply <u>mutatis mutandis</u> when the aqueous solubility is the minimum solubility in a pH range of 3.0-9.5.

In embodiments of particular interest a composition according to the invention contains one or more antiherpes virus agent(s) as an active substance. Relevant antiherpes virus agents are mentioned above and acyclovir is of particular importance. Acyclovir (9-[2-hydroxyethoxy)methyl]-guanine, an acyclic analogue to the natural nucleoside 2'-deoxyguanosine, is a widely used agent in the treatment of herpes virus infections. Compositions for oral, topical and intravenous administration are available. The delivery characteristics of acyclovir following administration by these routes are, however, far from being optimal probably due to the poor aqueous solubility and/or low lipophilicity of acyclovir. The solubility of acyclovir in water is about 1.5 mg/ml at 22°C and the partition coefficient (P) between octanol and 0.02 M phosphate buffer pH 7.4 (21°C) is about 0.03. In accordance with the physico-chemical

properties, the bioavailability after oral administration is rather low (about 15-20%) and highly variable and the percutaneous penetration is poor.

The active substance of low solubility is normally present in the composition in an amount in the range of from 1-20% by weight, usually 1-15% by weight.

A preferred composition according to the invention is a composition in which the active substance is acyclovir, the second substance is a the fatty acid ester and a liquid medium is present in the composition. In such compositions the fatty acid ester is preferably a glycerylmonooleate product having a glycerylmonooleate content of at least 88% such as, e.g., at least about 89, 90%, 91% or 92% by weight and a content of saturated monoglycerides of at the most 4% by weight such as, e.g., at the most about 2% by weight.

Preferred acyclovir-containing compositions according to the invention normally has a weight ratio between the glycerylmonooleate and the liquid medium is in the range between 1:0.3 and 1:2 such as between 1:0.5 and 1:1.5 such as, e.g. 1:1. In those cases where a structurant is present, the weight ratio between the combination of the glycerylmonooleate and the structurant, and the liquid medium is generally in the range between 60:40 and 75:25 such as between 63:37 and 73:27.

In such compositions, preferred structurants are Epikuron 200 and Vitamin E TPGS and combinations thereof and the weight ratio between Epikuron and Vitamin E TPGS may be between about 1:0.5 and 1:2 such as, e.g., between 1:0.75 and 1:1.5 such as, e.g., about 1:1.

Another preferred acyclovir-containing composition comprises glycerylmonooleate as second substance, a mixture of Epikuron 200 and Vitamin E TPGS as structurants, and water as a liquid medium and the concentration of Epikuron 200 is generally in a range of from 1%-25% by weight, the concentration of Vitamin E TPGS is in a range of from 1%-25% by weight, and the concentration of water is in a range of from 20%-40% by weight based on the total composition.

An interesting acyclovir-containing composition may also be presented as a precursor composition, wherein the weight ratio between fatty acid ester and any liquid medium present in the composition is between 50:50 and 100:0 such as between 60:40 and 99:1, between 70:30 and 90:10.

In such precursor composition, the weight ratio between the sum of the glycerylmonooleate and any structurant(s), and any liquid medium present in the composition is between 90:10 and 99:0.5, such as between 90:10 and 99:1.

In precursor compositions a liquid medium like e.g. water or glycerol, or a mixture of water and glycerol may be present. If the liquid medium is water containing glycerol, the glycerol:water ratio may be up to about 2.5:1 by weight, such as up to corresponding to a glycerol:water ratio of 1.5:2 such as, e.g., a ratio of about 1:1, 0.5:1, or 0.25:1.

Other interesting compositions are compositions comprising glycerylmonooleate, phosphatidylcholine (or Vitamin E TPGS) and, optionally, water and the weight ratio between the content of phosphatidylcholine (or Vitamin E TPGS) and glycerylmonooleate is at the most 1, such as e.g. 1:1, 1:2 or 1:4. In such compositions water may be present in a concentration of at the most 40% w/w based on the total composition.

Although the active substances of relatively low solubility as discussed above are of particular importance for use in compositions according to the invention, the invention is not limited to such active substances. Thus, in other aspects of the invention the active substance can in principle be any active substance irrespective of its solubility.

Lipophilicity of the active substance

The active substance may have any degree of lipophilicity. In certain interesting compositions, the active substance is one which has a lipophilicity of at the most 100, such as at the most, e.g., 75, 50, 25, 10, 7.5, 5 or 2.5, expressed as the partition coefficient between octanol and 0.05M phosphate buffer, pH 7, at 20°C, in some a partition coefficient of at the most 10 or even at the most 1 or at the most 0.75, 0.5, 0.1, 0.075, 0.05 or 0.04.

Alternatively, the lipophilicity may be expressed as the partition coefficient between octanol and an appropriate buffer having a pH corresponding either to the pH of the liquid crystalline phase or to the pH at which the active substance has its minimum solubility. In such cases, the values mentioned above are also valid.

Factors influencing the absorption or penetration of the active substance

It is known that the active substance must have balanced properties with respect to aqueous solubility and partition coefficient.

With respect to percutaneous absorption of active substances the vehicle in which the active substance is located is of importance. Thus, the affinity of the active substance to the vehicle compared with that of the active substance to the skin or the rate-limiting barrier of the skin must be of a less order of magnitude as the active substance otherwise would predominantly would be maintained in the vehicle and only slowly be released from the vehicle and penetrate the skin and thus enable the active substance to reach the target for the disease. Initial studies performed by the inventor show that vehicles on which compositions according to the invention are based readily releases the active substances tested (e.g. acyclovir) so that the active substances are available for penetration, i.e. a balanced affinity (vehicle/skin) has been obtained in these compositions.

Release of active substance from a composition according to the invention

With respect to acyclovir, it is believed that a composition with improved release properties and which sticks better to the skin can improve the treatment when compared to prior art compositions such as Zovir® cream or Zovirax® cream. The object of the present invention has therefore inter alia been to develop a bioadhesive composition containing e.g. acyclovir or other antiherpes virus agents with improved release properties so that fewer daily applications are needed to produce the same therapeutic effect (bioequivalence) or even improve the therapeutic effect.

As appears in more detail in the Experimental section herein, the present inventors have developed compositions containing GMO/water 65/35% w/w with acyclovir (crystalline and micronized, respectively) added in a concentration of 1-40% w/w. Cubic liquid crystalline phases are obtained in these compositions as evidence by polarized light. The results indicate that acyclovir in the concentration range investigated does not ruin the cubic lattice, and that acyclovir probably is inert in the cubic system. The distribution of the drug crystals in the cubic liquid crystalline phase appears as a homogeneous distribution (observed by microscopy). The cubic liquid crystalline phase without drug is transparent and has a relatively high viscosity. It is cosmetically appealing. When acyclovir is added, the viscosity is increased with the concentration, especially for the micronized quality. When the crystalline quality is added, the composition becomes greyish white. When the cubic liquid crystalline phase is applied to human skin it "melts" (gets softer) and penetrates the skin.

Furthermore, the inventor has developed compositions wherein the GMO has been substituted by a structurant and/or by a pharmaceutically acceptable excipient. The release of acyclovir from such compositions is described in the Experiments. The results show that the structurant

and/or certain pharmaceutically acceptable excipients (as defined in the claims) do not significantly influence the release rate of acyclovir in a negative manner.

As mentioned above, Zovir® and Zovirax® cream containing 5% w/w acyclovir are presently the drugs of choice for the treatment of herpes simplex. In order to compare the release rate of acyclovir from Zovir® cream and a cubic liquid crystalline phase (GMO/water 65/35 % w/w) containing 5% w/w acyclovir, the release of acyclovir from these compositions was examined, cf. Example 16 herein. Comparing the rate constants it is seen that the release rate of acyclovir is about 5-6 times faster from the cubic liquid crystalline phase than from the Zovir® cream. Poor release properties of the Zovir® cream are most likely one of the reasons for its suboptimum therapeutic effect. The improved release properties from the cubic liquid crystalline phase must therefore be seen as a very promising result.

While the present invention is not to be limited to any theory, it is believed, and supported by experimental data reported herein, that the capability of the composition to release the active substance of very low water solubility and very low solubility in the liquid crystalline phase at very satisfactory release rates is due to some kind of efficient dissolution system for particles, such as crystals, of the active substance through the liquid medium "channels" of the liquid crystalline phase.

The performance of the compositions according to the invention with respect to releasing the active substance from the liquid crystalline phase can be adequately expressed by the slope of the cumulative release in µg as a function of the square root of the release time in hours in the release experiment defined in connection with Fig. 13 (in which the concentration of the substance is 5%). In preferred compositions according to the invention, the slope is at least 50, more preferred at least 100.

An expression of better performance is a slope of at least 200, such as at least 300, or at least 500 or even at least 700 or at least 900.

Concentration of active substance in a composition according to the invention

Important embodiments of the present invention are compositions in which the active substance is present in a concentration which is above the saturation concentration at 20°C so that part of the active substance, and in many cases the predominant proportion of the active substance, is present in the form of particles, such as, e.g., crystals. In such a case, normally at least 25%, such as at least 50%, by weight of the active substance present in the composition constitutes a proportion which is present above the saturation concentration at 20°C. Very valuable

compositions according to the invention are compositions, wherein at least 75%, such as at least 90% or even at least 95% or at least 98% by weight of the active substance present in the composition constitutes a proportion which is present above the saturation concentration at 20°C.

In general, the concentration of the active substance in the composition will depend on the condition to be treated or prevented and the desired or necessary administration frequency. The concentration of the active substance in a pharmaceutical composition depends on the nature of the second compound in question, its potency, the severity of the disease to be prevented or treated, and the age and condition of the patient. Methods applicable to selecting relevant concentrations of the active substance in the pharmaceutical composition are well known to a person skilled in the art and may be performed according to established guidelines for good clinical practice (GCP) or Investigational New Drug Exemption ("IND") regulations as described in e.g. Drug Applications, Nordic Guidelines, NLN Publication No. 12, Nordic Council on Medicines, Uppsala 1983 and Clinical Trials of Drugs, Nordic Guidelines, NLN Publication No. 11, Nordic Council on Medicines, Uppsala 1983, or CPMC/E.U. Guidelines for Good Clinical Practice 95/135. A person skilled in the art would, by use of the methods described in standard textbooks, guidelines and regulations as described above as well as common general knowledge within the field, be able to select the exact dosage regimen to be implemented for any active substance and dosage form using merely routine experimentation procedures.

Bioadhesiveness of the compositions according to the invention

As mentioned above, it is a great advantage of the compositions according to the invention that the second substance especially fatty acid esters can confer bioadhesiveness to the compositions. During the last decade increased attention has been given to the possibility of using bioadhesive/mucoadhesive polymers for drug delivery purposes. It is believed that several problems associated with conventional controlled release drug delivery systems may be reduced or eliminated by using a bioadhesive/mucoadhesive drug delivery system. In conventional controlled release drug delivery systems no precautions are made in order to localize the delivery system after administration and, furthermore, the contact time in vivo between the drug delivery system and a particular site is often so short that no advantages are to be expected with respect to, e.g., modifying tissue permeability. Compared with conventional controlled release drug delivery systems, bioadhesive drug delivery systems are believed to be beneficial with respect to the following features:

i) a bioadhesive drug delivery system localizes a drug substance in a particular region, thereby improving and enhancing the bioavailability for drug substances which may have poor bioavailability in themselves,

ii) a bioadhesive drug delivery system leads to a relatively strong interaction between a bioadhesive substance and a mucosa; such an interaction contributes to an increasing contact time between the drug delivery system and the tissue in question and permits localization of the drug delivery system to a specific site,

iii) a bioadhesive drug delivery system is contemplated to prolong delivery of drug substances in almost any non-parenteral route,

iv) a bioadhesive drug delivery system can be localized on a specific site with the purpose of local therapy e.g. treatment of local fungal diseases, permeability modification, protease and other enzyme inhibition, and/or modulation of immunologic expression,

v) a bioadhesive drug delivery system may be targeted to specific diseased tissues, and

vi) a bioadhesive drug delivery system may be employed in those cases where the conventional approach to controlled release drug delivery is unsuitable, i.e. for certain drug substances or classes of drug substances which are not adequately absorbed.

Thus, preferred compositions according to the present invention are compositions in which the second substance like a fatty acid ester or combination of fatty acid esters present in the composition complies with the requirements of bioadhesion defined herein when tested for bioadhesion in an in vivo model or any other bioadhesivity model as given in the experimental section herein. Especially preferred are compositions which in themselves comply with the requirements of bioadhesion defined herein when tested for bioadhesion in an in vivo model or other bioadhesivity model as given in the experimental section herein.

Thus, interesting compositions are compositions in which the second substance like e.g. a fatty acid ester or combination of fatty acid esters optionally in combination with the structurant, when tested in a bioadhesive test system, comprising:

i) placing a segment of longitudinally cut rabbit jejunum on a stainless steel support in such a manner that the mucosa layer of the jejunum is placed upside so as to allow application of said second substance and any structurant,

ii) placing the resulting support at an angle of -21° ± 2° in a cylindrical cell thermostated at 37°C ± 0.5°C and with the relative humidity kept at about 100%,

iii) flushing the jejunum on the support with 0.02M isotonic phosphate buffer solution (pH 6.5, 37°C) for 5 min at a flow rate of 10 ml/min,

iv) applying an accurately weighed amount of a sample of said second substance and any structurant (about 100 mg) on a surface area (about 0.8 x 6 cm) of the mucosa of the jejunum on the support,

v) dropping about 0.5 ml of said phosphate buffer solution on the sample applied,

vi) leaving the resulting sample from step v) for 10 minutes in said cell to allow the sample to interact with glycoproteins of the jejunum,

vii) flushing the jejunum with the sample applied with said phosphate buffer solution (pH 6.5, 37°C) for 30 minutes at a flow rate of 10 ml/min,

viii) collecting the washings resulting from step vii), and

ix) calculating the residual amount of the sample remaining on the jejunum by measuring the amount of the sample in the washings or by measuring the amount remaining on the jejunum,

results in a residual amount of at least 60% w/w, in particular a residual amount of at least 70% w/w, such as at least 80% w/w, preferably at least 85% w/w and more preferably at least 90% w/w.

Interesting compositions are also compositions as defined further above which, when tested in the jejunum test system defined in claim above, result in a residual amount of at least 40% w/w of the second substance such as a fatty acid ester or combination of fatty acid esters or at least 40% w/w of the active substance.

A measure of the bioadhesivity of a composition itself is that it complies with the requirements for bioadhesion defined herein when tested for bioadhesion in the in vivo model described herein involving testing the rinsing off ability from skin.

As mentioned above, the biopharmaceutical properties of a composition according to the invention are not significantly changed by adding a structurant or a pharmaceutically-acceptable excipient. Thus, the score obtained in the test for bioadhesion (washing off ability from the skin) is substantially of the same order of magnitude as would have been obtained for a comparative composition wherein the structurant(s) and/or pharmaceutically acceptable excipient has(have) been replaced with the same amount by weight of said second substance.

As evidenced in the Examples herein, an active substance does not significantly influence the bioadhesive properties of a vehicle provided that the concentration of the active or protective substance is relatively low such as at the most about 10-15% w/w or at the most about 8-10% w/w. The kind of active substance (structure, molecular weight, size, physico-chemical properties, loading, pKa, solubility, etc.) will of course be responsible for the maximal concentration which can be incorporated in the vehicle without significantly affecting the bioadhesive properties of the composition. In the Examples herein, it is also demonstrated that the active substance locates in the liquid crystalline phase of the fatty acid ester and most likely the solubility of the active substance in this phase has impact on the bioadhesive properties as well as on the release properties of the composition.

Administration routes and pharmaceutical compositions

As mentioned above, the application is intended for skin or mucosa. Other applications may of course also be relevant such as, e.g., application on dentures, prostheses and application to body cavities such as the oral cavity. The mucosa is preferably selected from oral, nasal, aural, lung, rectal, vaginal, and gastrointestinal mucosa.

A bioadhesive composition for administration according to the invention may in special cases also be in the form of a multiple unit composition, in the form of, e.g., a powder. A multiple unit composition may be administered to skin or mucosa, preferably the mucosa is selected from oral, nasal, rectal, aural, vaginal, lung, and gastrointestinal mucosa. Most preferred is a bioadhesive composition intended for administration to the gastrointestinal tract.

Bioadhesive compositions according to the invention for application on skin and especially to wounds may in certain cases comprise a polysaccharide in a concentration of at least 15% w/w, calculated on the total weight of the composition. The polysaccharide is preferably selected from the group consisting of carmelose, chitosan, pectins, xanthan gums, carrageenans, locust bean gum, acacia gum, gelatins, alginates, and dextrans, and salts thereof. The compositions are easy to apply on the wound and are believed to be able to extract water from the wound and thereby drying the wound.

Apart from the active or protective substance and the bioadhesive fatty acid ester substance, the bioadhesive compositions for use according to the invention may comprise pharmaceutically or cosmetically acceptable excipients or additives normally used in pharmaceutical compositions.

The bioadhesive compositions may be in form of, e.g., a spray, a solution, a dispersion, a suspension, an emulsion, powders, gels including hydrogels, pastes, ointments, creams, drenches, delivery devices, suppositories, enemas, implants, aerosols, microcapsules, microspheres, nanoparticles, liposomes, dressings, bandages, plasters, tooth paste, dental care compositions, and in other suitable form.

The bioadhesive compositions may be formulated according to conventional pharmaceutical practice, see, e.g., "Remington's Pharmaceutical Sciences" and "Encyclopedia of Pharmaceutical Technology", edited by Swarbrick, J. & J. C. Boylan, Marcel Dekker, Inc., New York, 1988.

Pharmaceutically acceptable excipients for use in bioadhesive compositions for use according to the invention may be, for example,

inert diluents or fillers, such as sucrose, sorbitol, sugar, mannitol, microcrystalline cellulose, carboxymethylcellulose sodium, methylcellulose, hydroxypropyl methylcellulose, ethylcellulose, starches including potato starch, calcium carbonate, sodium chloride, lactose, calcium phosphate, calcium sulfate or sodium phosphate; and

lubricating agents including glidants and antiadhesives, for example, magnesium stearate, zinc stearate, stearic acid, silicas, hydrogenated vegetable oils or talc.

Other pharmaceutically acceptable excipients can be colorants, flavouring agents, plasticizers, humectants, buffering agents, solubilizing agents, release modulating agents, etc.

For application to the rectal or vaginal mucosa suitable compositions for use according to the invention include suppositories (emulsion or suspension type), solutions, enemas, and rectal gelatin capsules (solutions or suspensions). Appropriate pharmaceutically acceptable suppository bases include cocoa butter, esterified fatty acids, glycerinated gelatin, and various water-soluble or dispersible bases like polyethylene glycols and polyoxyethylene sorbitan fatty acid esters. Various additives like, e.g., enhancers or surfactants may be incorporated.

For application to the nasal mucosa, nasal sprays and aerosols for inhalation are suitable compositions for use according to the invention. In a typically nasal formulation, the active ingredients are dissolved or dispersed in a suitable vehicle. The pharmaceutically acceptable

vehicles and excipients and optionally other pharmaceutically acceptable materials present in the composition such as diluents, enhancers, flavouring agents, preservatives etc. are all selected in accordance with conventional pharmaceutical practice in a manner understood by the persons skilled in the art of formulating pharmaceuticals.

For application to the oral cavity, teeth, skin or nail, the compositions for use according to the invention may contain conventionally non-toxic pharmaceutically acceptable carriers and excipients including microspheres and liposomes. The formulations include creams, ointments, lotions, liniments, gels, hydrogels, solutions, suspensions, sticks, sprays, pastes, dressings, bandages, plasters, tooth paste, dental care compositions, and the like. The pharmaceutically acceptable carriers or excipients may include emulsifying agents, stabilizing agents, antioxidants, buffering agents, preservatives, humectants, penetration enhancers, chelating agents, gelforming agents, ointment bases, perfumes and skin protective agents.

Examples of emulsifying agents are naturally occurring gums, e.g. gum acacia or gum tragacanth, naturally occurring phosphatides, e.g. soybean lecithin and sorbitan monooleate derivatives.

Examples of antioxidants are butylated hydroxy anisole (BHA), ascorbic acid and derivatives thereof, α-tocopherol and derivatives thereof, vitamin E, salts of sulphur dioxide, cysteine, citric acid, ascorbyl palmitate, butylhydroxytoluene, complexing agents, chelating agents, sodium pyrosulfite, EDTA and gallic acid esters.

Examples of preservatives are parabens, such as methyl, ethyl, propyl p-hydroxybenzoate, butylparaben, isobutylparaben, isopropylparaben, potassium sorbate, sorbic acid, benzoic acid, methyl benzoate, phenoxyethanol, bronopol, bronidox, MDM hydantoin, iodopropynyl butylcarbamate, EDTA, propyleneglycol (increases the solubility of preservatives) benzalconium chloride, benzylalcohol, chlorhexidine diacetate, chlorhexidine digluconate, chlorbutol, phenetanol, phenols (phenol, o-cresol, p-cresol, chlorcresol, tricresol), alkanols (chlorbutanol, phenetanol), sorbic acid, and mercuri-compounds like e.g. phenylmercurinitrate.

Examples of humectants are glycerin, propylene glycol, sorbitol and urea.

Examples of suitable release modulating agents for use according to the invention are glycerol, sesame oil, soybean oil, lecithin and cholesterol.

Examples of penetration enhancers are oleic acid, propylene glycol, DMSO, triethanolamine, N,N-dimethylacetamide, N,N-dimethylformamide, 2-pyrrolidone and derivatives thereof, tetrahydrofuryl alcohol and Azone.

Examples of chelating agents are sodium EDTA, citric acid and phosphoric acid.

Examples of other excipients for use in compositions for use according to the invention are edible oils like almond oil, castor oil, cacao butter, coconut oil, corn oil, cottonseed oil, linseed oil, olive oil, palm oil, peanut oil, poppyseed oil, rapeseed oil, sesame oil, soybean oil, sunflower oil, and teaseed oil; and of polymers such as carmelose, sodium carmelose, hydroxypropylmethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, chitosane, pectin, xanthan gum, carrageenan, locust bean gum, acacia gum, gelatin, and alginates, and solvents such as, e.g., glycerol, ethanol, propylene glycol, polyethylene glycols such as PEG 200 and PEG 400, Pluronic, polysorbate, and ethylene glycol.

Examples of ointment bases are beeswax, paraffin, cetyl palmitate, vegetable oils, sorbitan esters of fatty acids (Span), Carbopol, polyethylene glycols, and condensation products between sorbitan esters of fatty acids and ethylene oxide, e.g. polyoxyethylene sorbitan monooleate (Tween).

A most important composition according to the invention is one in which the antiviral substance is acyclovir. Examples of important embodiments hereof and of other compositions according to the invention containing nucleosides of low solubility as defined herein are claimed in the claims are described in detail in the Examples.

Furthermore, relevant compositions and conditions to be fulfilled for the individual components in the compositions are claimed in the claims and described in the Examples.

Other aspects of the invention

The invention also relates to methods for preparing the compositions according to the invention. Details concerning the preparation are given in the Examples herein. Furthermore, the invention also relates to a method for administering an active substance to e.g. a human, the method comprising administering to the human in need thereof a therapeutically and/or prophylactically effective amount of the active substance in a pharmaceutical composition according to the invention.

As will be understood, details and particulars concerning the composition aspects of the invention will be the same as or analogous to the details and particulars concerning the other

aspects of the invention and the method aspects discussed above, and this means that wherever appropriate, the statements above concerning a pharmaceutical composition, a second-substance, a structurant, a liquid medium and a pharmaceutically acceptable excipient, as well as improved properties and uses apply mutatis mutandis to all aspects of the invention.

MATERIALS

Glycerylmonooleate (monoolein), manufactured by Grindsted Products A/S, Denmark

DIMODAN® GMO-90, a distilled monoglyceride

Chemical and physical data

Monoester content	min. 95%
Diglycerides	max. 3%
Triglycerides	max. 0.2%
Free fatty acids	max. 0.5%
Free glycerol	max. 0.5%
Iodine value	approx. 72
Fatty acid composition:	
Oleic acid	92%
Linoleic	6%
Saturated (C_{16}/C_{18})	2%
Melting point	35-37°C
Antioxidants and synergists added:	
Ascorbyl palmitate	max. 200 ppm
α-Tocopherol	max. 200 ppm
Citric acid	max. 100 ppm

In the following examples, the term "GMO-90" indicates that the above-mentioned glycerol monooleate product is employed, except where otherwise stated.

Another quality of glycerol monooleate has been employed in some of the following examples, namely

RYLO® MG19 (with a content of about 90% GMO) manufactured by Danisco Ingredients, Denmark

Chemical and physical data

Monoester content	min. 95%
Free fatty acids	max. 0.5%
Free glycerol	max. 1%
Iodine value	approx. 72

Fatty acid composition:

Oleic acid	>90%
Linoleic and linolenic acids	<6%

Antioxidants and synergists added:

Ascorbyl palmitate	max. 200 ppm
α-Tocopherol	max. 200 ppm
Citric acid	max. 100 ppm

<u>Glycerylmonooleate</u> 84% "GMO-84" (monoolein), manufactured by Grindsted Products A/S, Denmark; the product used has a total content of fatty acid monoesters of at least about 96%. The product employed in the examples described herein had the following composition of fatty acid monoesters:

Glycerylmonooleate	about 84% w/w
Glycerylmonolinoleate	about 7% w/w
Glyceryl monopalmitate	about 3% w/w
Glyceryl monostearate	about 4% w/w

In the following examples, the term "GMO 84" indicates that this glycerol monooleate product is employed.

Other commercially available glycerol monooleate products (e.g. Myverol 18-99 and GMOrphic 80 available from Kodak Eastman, U.S.A.) which differ in the composition of fatty acid monoesters compared with the products described above may also be applied.

<u>Glycerylmonolinoleate</u> (Dimodan® LS), manufactured by Grindsted Products A/S; the product used has a total content of fatty acid monoesters of at least about 90% such as about 96% w/w.

The product employed in the examples described herein had the following composition of fatty acid monoesters:

Glyceryl monopalmitate	about 6% w/w
Glyceryl monostearate	about 6% w/w
Glycerylmonooleate	about 22% w/w
Glycerylmonolinoleate	about 63% w/w

Other commercial available glycerylmonolinoleate products (such as, e.g., Myverol® 18-92 available from Kodak Eastman, U.S.A.) which differ in the composition of fatty acid monoesters compared with the product described above may also be applied.

<u>Phosphatidylcholine</u> (Epikuron available from Lucas Meyer, Hamburg, Germany):

Lipoid S100 or S75 (purified soya phosphatidylcholine available from Lipoid GmbH, Germany)

Epikuron 200 (purified soya phosphatidylcholine):

Phosphatidylcholine of soyabean origin

Characteristics: EPIKURON 200 is a purified phosphatidylcholine of soybean origin.

Composition: The product consists of phosphatidylcholine, a small amount of lyso-phosphatidylcholine and other phospholipids.

phosphatidylcholine	min. 92%
lyso-phosphatidylcholine	max. 3%
other phospholipids	max. 2%
moisture	max. 0.8%
oil content	max. 1.0%
α-Tocopherol	0.2%
fatty acids (total content) including:	
palmitic acid/stearic acid	16-22%
oleic acid	8-12%

linoleic acid	62-66%
linolenic acid	6-8%

Epikuron 145 V:

Deoiled, fractionated soybean lecithin

Characteristics: EPIKURON 145 V is a fractionated, wax-like soybean lecithin with enriched content of phosphatidylcholine for the use in pharmaceutical industry.

Composition: Mixture polar (phospho- and glyco-) lipids and a small amount of carbohydrates.

phosphatidylcholine	min. 45%
phosphatidylethanolamine	min. 10%
phosphatidylinositol	max. 3%
phosphatidic acid	max. 3%
lyso-phosphatidylcholine	max. 4%
other phospholipids	max. 18%
glycolipids	max. 15%
moisture	max. 0.6%
oil content	max. 2.0%
α-Tocopherol	0.2%
fatty acids (total content) including:	
palmitic acid/stearic acid	18-22%
oleic acid	6-10%
linoleic acid	62-66%
linolenic acid	6-8%

Miconazol base available from MedioLast SPA, Milano, Italy
Lidocaine hydrochloride available from Sigma Chemical Co., St. Louis, U.S.A.
Lidocaine base available from Sigma Chemical Co., St. Louis, U.S.A.
Acyclovir (crystalline) available from Chemo Iberica, Spain, e.g. a quality where 90-100% of the crystals have a particle size of less than 100 μm

Acyclovir (micronized) available from Chemo Iberica, Spain, e.g. a quality where 100% of the particles have a particle size under 24 μm and not less than 90% under 12μm

Ethanol available from Danisco A/S, Denmark, complies with the DLS standard (98.8-100% w/w ethanol)

Sesame oil available from Nomeco, Denmark

Soybean oil available from Nomeco, Denmark

Glycerol available from Joli Handel ApS, Denmark

Lecithin Epikuron 200 or Epikuron 145 from Lucas Meyer

Benzyl alcohol available from Merck AG, Germany

Water, purified or distilled water

DEAE-dextran (MW = 500,000) available form Sigma Chemical Co., St. Louis, U.S.A.

Sodium alginate (Sobalg FD 120) available from Grindsted Products A/S, Denmark

Hydroxypropylmethylcellulose (Methocel K15MCR Premium USP) available from Colorcon Limited, U.S.A.,

Carbopol 934 available from The BFGoodrich Company, U.S.A.

Vitamin E TPGS (d-α-tocopherylpolyethyleneglycol 1000 succinate) available from Kodak Eastman (in the following designated TPGS)

Aspirin available from Sigma, Chemical Co., St. Louis, U.S.A.

Propylene glycol available from BASF Aktiengesellschaft, Germany

α-tocopherol available from BASF Aktiengesellschaft,, Germany

Paraffin oil available from Unichem, Denmark

Polyethylene glycol 200 available from Unichem, Denmark

Lactose available from Inkem

Hydroxypropylcellulose available from Aldrich Chemical Company, U. S. A.

Lanolin available from Westbrook Lanolin Company

Sorbitan ester available from Maximex ApS, Denmark

Heating and cooling stage, Linkam Peltier Stage and Controller, PE 60 for microscope

Ultra-Turrax T25 homogenisator

400 Watt Ultrasonic Processors VCX 400

Coulter Multisizer II (Coulter), Malvern 2600 droplet and particle size analyse (for the determination of particle size distribution).

Strölein Areameter and Coulter SA3100 for the determination of the surface area of the particles.

METHODS

Test systems for bioadhesion

1. In vitro test system for bioadhesion by means of rabbit jejunum membranes

The test system for bioadhesion described in the following is a modified system of a method described by Ranga Rao & Buri (Int. J. Pharm. 1989, 52, 265-270).

Male albino rabbits (3-4 kg, New Zealand white rabbit SSC: CPH) were fasted for 20 hours before they were killed by means of a pentobarbital sodium injection. The intestines of the rabbits were dissected and placed in an isotonic 0.9% sodium chloride solution at room temperature (about 18°C). Within 30 minutes the jejunums were cut and washed with 0.9% sodium chloride solution. The lumens were gently rinsed with the saline until the intestines were clean. The jejunums were cut into pieces of about 8-9 cm in length and frozen (-20°C) immediately. The jejunums were stored up to 3 months before use (when performing the test described below it was found that the use of fresh jejunum or, alternatively, jejunum which had been frozen for up to 3 months gave reproducible and significantly similar results). Before testing, the segment of jejunum was gently thawed out.

The segment of the jejunum was cut longitudinally. It was placed on a stainless steel support (a tube of 2 cm in diameter and cut longitudinally at an axis parallel to its centre) with the mucosa layer upside, spread and held in position on the support by the adhesive effect of the jejunum itself. The support with the jejunum was placed at an angle of from about -5° to about -25° such as -7° or -21° (in the Examples the angle applied is denoted "angle" in a cylindrical cell thermostated at 37°C. A schematic illustration of the cell is shown in Fig. 1. The relative humidity in the thermostated cell was kept at about 100%. The jejunum was then flushed with a medium of 0.02M isotonic phosphate buffer solution (pH 6.5, 37°C) for 2 or 5 minutes (in the following denoted "initial rinsing period") at a flow rate of 5 or 10 ml/min (in the following denoted "initial rinsing flow"), respectively, using a peristaltic pump to equilibrate the jejunum with the buffer and to rinse off loose mucosa. [Immediately before application of the sample, the support was positioned at a horizontal position and after application the position was changed to the initial position of -21°.] An accurately weighted amount of the sample to be tested for bioadhesive properties (about 50-150 mg) was placed evenly on the mucosa of the jejunum (about 0.8 x 6 cm). About 1 ml of the buffer solution was carefully dropped evenly on the sample applied to ensure formation of such a liquid crystalline phase, if possible (in the case of monoolein, the liquid crystalline phase may be the cubic, hexagonal, reverse hexagonal, micellar, reverse micellar, or lamellar phase). [In those cases where the viscosity of the test sample are

relatively high or where a precipitation has taken place, the test sample is gently melted on a heating plate or in an oven at a temperature of max. 60°C in the case of GMO or GML and cooled to a temperature of at the most about 40°C before application on the rabbit jejunum.] Immediately after, the segments were left for 5-20 minutes such as, e.g., 10 minutes in the cell allowing the sample to interact with the glycoproteins of the jejunum and to prevent drying of the mucus. After 10 minutes, the segments were flushed evenly with the isotonic 0.02M phosphate buffer solution (pH 6.5, 37°C) for 15-60 minutes such as, e.g., 30 minutes at a flow rate of 5-15 ml/min such as 10 ml/min (in the Examples denoted "flow rate"). The tip of the tube carrying the buffer solution was placed 3-4 mm above the jejunum to ensure an even liquid flow over the mucosa. The washings were collected into a beaker. The amount of bioadhesive component remaining on the jejunum was calculated either by measuring the amount of sample in the beaker or by measuring the amount of sample remaining in the jejunum by means of a suitable analysis method, e.g. HPLC.

At the end of the experiment, the remaining sample on the jejunum was checked with a pair of tweezers to reveal false positive results.

In 1-2 test run(s) out of 10, false negative results were observed probably due to a loose mucosa layer on the rabbit jejunum.

During testing and validation of the method, the parameters given above were varied (e.g. the angle applied, the flow rate, the amount applied, etc.). In order to exclude false negative and false positive results it was found that the following conditions were satisfactory:

Time for prehydration before application of sample:	10 min
Amount applied:	about 50-150 mg (tests have shown that a variation in the amount applied within a range of from about 25 mg to about 225 mg was without significant influence on the results obtained)
Angle:	-21°
Flow rate:	10 ml/min
Flow period:	30 minutes (it was found that a flow period of at least 10 minutes gives reproducible results and a prolongation of the period to about 60 minutes does not significantly change the result)

Furthermore, it was found advantageous that the method allows rinsing of the sample applied on the jejunum by an aqueous medium, thus allowing a liquid crystalline phase to be formed. The method also permits application of fluid samples and pellets.

Determination of the bioadhesiveness of a test sample

In those cases where the test sample is a second substance like a fatty acid ester optionally in combination with a structurant, the substance(s) is/are considered as bioadhesive if the residual amount is at least about 60% w/w such as at least about 65% w/w, about 70% w/w, about 75% w/w, about 80% w/w, about 85% w/w, 90% w/w, or about 95% w/w.

In those cases where the test sample is a composition comprising a combination of a second substance like e.g. a fatty acid ester and an active substance and, optionally, other substances like structurant and/or excipients, the composition is considered bioadhesive if the residual amount (of the second substance like e.g. the fatty acid ester, or the active substance) is at least about 40% w/w such as at least about 45% w/w, about 50% w/w, 55% w/w, 60% w/w, 65% w/w, 70% w/w, 75% w/w, or 80% w/w.

In the present context evaluation of the bioadhesive properties of a substance may also be performed by use of the test system and test conditions described above but modified with respect to type of membrane, amount applied of test sample, test angle, flow rate, medium, etc. In this connection, tests have been performed in order to evaluate the influence of different membranes on the test results. The following results were obtained using the above-mentioned test conditions (angle: -21°, flow rate: 10 ml/min, and flow period: 30 min) and applying GMO on the membrane:

Membrane % w/w	Bioadhesion Residual amount %
rabbit jejunum	90
pig ileum	106*
pig stomach	106*
buccal pig mucosa	88

* the high result is most likely due to an interference from the intestines or the stomach

2. In vitro test system for bioadhesion by means of tensiometry

The test system for bioadhesion described in the following is a modified system of a method described by Tobyn, M., J. Johnson & S. Gibson (in "Use of a TA.XT2 Texture Analyser in Mucoadhesive Research", International LABMATE, 1992, XVII (issue VI), 35-38).

The test system involves measuring the tensile force required to break an adhesive bond formed between a model membrane and a test sample (i.e. the sample which is tested for its bioadhesive properties).

The test apparatus employed in the following is a TA.XT2 Texture analyser (Stable Micro System Ltd., Haslemere, UK) (Fig. 2) equipped with a 5 kg load cell interfaced with an IBM PC computer running XT-RA dimension software, DOS version. The test enables measuring the strength of adhesive bonding established by contacting a model membrane, i.e. in this case a pig intestine segment, and the test sample. An analogous test apparatus may also be employed.

The TA.XT2 Texture analyser apparatus is equipped with an instrument probe 1 (see Fig. 2) which is movable in a vertical direction at a variable rate. During the so-called withdrawal phase of the testing, the instrument probe is moved upwards with a constant rate until detachment occurs (see below). Furthermore, the apparatus is equipped with a stationary plate 2 on which a first holder 3 is placed. Before and during a test run, a model membrane 4 is fixed on this holder, e.g. by means of a cap or double adhesive tape or glue. The area exposed to the test may be determined by the area of the probe (preferred in this case) or by the area of the test samples (e.g. a coated cover glass), or by the area of a holder fixed to the probe. The accurate size of the exposed area is used in the calculation of the adhesive strength (see below).

As mentioned above, the test involves employment of a model membrane, primarily of animal origin. The membrane could be e.g. rabbit, rat or pig gastric mucosa; a segment of rabbit, rat or pig intestines, e.g. a segment of rabbit jejunum; a segment of rabbit or porcine buccal mucosa; or a segment of rabbit, rat or pig intestines from which the mucosal layer has been removed prior to testing; or skin from an animal (after removal of substantially all subcutaneous fat); or it could be artificially or commercially available mucin.

In the tests described below, duodenum, jejunum and the upper part of ileum from freshly slaughtered pigs were used. The gut was stored on ice until it was washed with 0.9% w/w sodium chloride solution within 2 hours. The lumens were gently rinsed with the saline until the intestines were clean. The gut was cut into pieces of 3-4 cm and immediately frozen (-20°C). The intestines were stored up to 2 months before use. Before testing, the segments were gently thawed out. The gut segment was opened along the mesenteric border. Serosa and muscularis layers were removed by stripping with a pair of tweezers, taking care to maintain the integrity of the mucus layer. This resulted in a flattening of the originally folded mucosal surface. Before use the tissue was equilibrated in the testing medium for about 10 min, which was sufficient for the tissue to attain temperature and pH equilibrium as measured by pH paper.

If the results obtained by use of another membrane than the one mentioned above are compared to the bioadhesive properties of various substances or combinations, the results of a reference compound could be included. As discussed below testing of a reference sample may also be made as a routine. Polycarbophil and Carbopol 934 have been found suitable as reference compounds.

An accurate amount of a test sample (about 25-500 mg) is applied in a uniform layer either

i) on the luminal side of the model membrane placed on the first holder,

ii) directly on the instrument probe, if necessary by means of a cap, a double adhesive tape or glue applied on the instrument probe before application of the test sample,

iii) on a cover glass which is placed on the instrument probe with the test sample pointing downwards, or

iv) via a probe modified in such a manner that it allows application of a relatively low viscous or semi-solid sample, the modified probe also allows the necessary addition of an aqueous medium.

In those cases where it is not possible to fix the test sample to the instrument probe, the apparatus may be equipped with a second holder 5 on which another model membrane is fixed. In such cases, the model membranes employed on the two holders are usually of the same type. It is also possible to fix the other model membrane directly to the instrument probe e.g. by means of a double adhesive tape, glue, or a cap.

For an adhesion test, a tissue (porcine intestinal mucosa) of about 3 x 3 cm was fixed on the tissue holder 3 with the mucosa layer upside. Before application of the tissue, a piece of gauze was placed directly on the tissue holder, and thereupon the tissue was placed. This precaution is made in order to stabilize the contact force. In order to moist the tissue and hydrate the sample, about 0.5 ml isotonic 0.05M phosphate buffer, pH 6.0, was added to the tissue. Such an addition also enables a cubic phase to be formed. The instrument probe with sample (e.g. applied by smearing 50-80 mg of the sample onto the probe in a thin, smooth layer, see below) was lowered with a test speed of 0.1 mm/sec in order to bring the tissue and the sample in contact under a constant force. The contact area was either 1.33 cm^2 (cover glass) or 1.27 cm^2 (probe) depending on the method of sample preparation. The contact force was set to 0.2N and the contact time was 30 min. After 30 min the probe was withdrawn with a rate of 0.1 mm/sec (post test speed) for 10 mm. Initial experiments showed that this distance was well beyond the point where the sample and mucous separated during withdrawal.

The peak detachment force and the area under the force/time curve was calculated automatically using the XT-RA dimension software. The work of adhesion (mJ cm^{-2}), said to be the most accurate predictor of mucoadhesive performance, was calculated.

Sample preparation

Application method of the polymers used as reference:

Cover glasses having a diameter of 13 mm (area 1.33 cm^2) were coated with the polymers under investigation by pipetting 100 µl of a 1% w/w solution of methanol or water in the center of the glass plate. After drying for 2 hours at 60°C in an oven, a thin polymer film remained. One cover glass was attached to the probe (diameter of 12.7 mm) with its non-coated side by means of double adhesive tape.

Cover glasses and mucosa were only used once (i.e. for one measurement).

Application of compositions:

A. Melting (if possible) of the solid or semi-solid composition and dipping the probe into it (this method is only used if the melting procedure does not change the properties of the composition). The sample (25-100 mg) was applied to the probe in a smooth layer by dipping the probe into melted GMO. The sample was solidified at room temperature or, if necessary, by cooling.
B. Smearing 25-100 mg of the sample directly on the probe.
C. Fixing the sample by means of a cap, double adhesive tape, or glue

Test runs are performed after the tissue has equilibrated in an aqueous medium at room temperature for 5-20 min. Then the tissue was removed from the aqueous medium and placed in the test apparatus and then the test was run.

In some cases, variations of the above-given method may be relevant, e.g. running the test in an aqueous medium or running the test at a temperature different from room temperature such as 37°C.

Furthermore, the test parameters may be varied, e.g. as follows:

Hydration time:	0 - 20 min
Contact time:	60 sec - 50 min

Contact force: 0.05-0.4N
Equilibration medium
Test speed: 0.02-1 mm/sec
Post test speed: 0.02-1 mm/sec

Test run temperature may be changed by employing a suitable temperature controlled oven such as a SMTC/04 from Stable Microsystems, Haslemere, UK.

Determination of the bioadhesive properties of a test sample

In order to test whether a test sample is bioadhesive, two test runs are performed:

1. A test run with the test sample applied (result: work of adhesion WA_S),

2. A test run with a known and excellent bioadhesive sample (e.g. polycarbophil) (result: work of adhesion WA_R).

In both cases the work of adhesion is calculated and the test sample is considered bioadhesive if WA_S/WA_R x 100% is at least 30%, such as 35%, 40%, 45%, 50%, or 55%. In general, a sample is graded to be a weak bioadhesive if the result is less than about 30%, a medium bioadhesive if the result is about 30%-50%, a strong bioadhesive if the result is at least 50%.

Polycarbophil (Noveon™ AA-1, BF Goodrich, Hounslow, U.K.) is a high molecular weight poly(acrylic acid)copolymer loosely cross-linked with divinyl glycol. On account of its known excellent mucoadhesive properties, this polymer serves as a reference. Before testing in the above-mentioned tensiometric test, a polycarbophil gel is prepared by mixing polycarbophil with water or methanol (resulting concentration about 10-20 mg ml^{-1}) and the mixture is allowed to hydrate at room temperature for 24 hours. The polymer solution is periodically stirred. The resulting gel is applied on a cover glass and tested as described above and the result obtained is used as a reference value for excellent bioadhesive substances.

Similarly, other substances which are known bioadhesive substances are tested such as, e.g., chitosane, tragacanth, hydroxypropylmethylcellulose (HPMC), sodium alginate, hydroxypropylcellulose (HPC), karaya gum, carboxymethylcellulose (CMC), gelatin, pectin, acacia, PEG 6000, povidone, or DEAE-dextran (less bioadhesive than polycarbophil). By choosing test substances with various degrees of bioadhesiveness, an evaluation scale can be made and the performance of a test sample with respect to bioadhesiveness can be evaluated. It is contemplated that the following scale is applicable provided the test conditions given above are

applied. It is clear that if the test conditions are changed, another scale may be more relevant. A suitable scale is then to be based on the values obtained for the excellent bioadhesive polycarbophil and the weak bioadhesive such as DEAE-dextran.

Bioadhesive properties	Work of adhesion (mJ cm^{-2})
none	less than 0.005
poor	about 0.005 - about 0.012
moderate	about 0.012 - about 0.020
good	about 0.020 - about 0.04
excellent	more than 0.04

When testing some known bioadhesive substances and GMO, the following results were obtained as a mean of six experiments:

Test substance	Work of adhesion (mJ cm^{-2})
DEAE-dextran	0.010
Sodium alginate	0.015
GMO 84/water 85/15% w/w*	0.028
HPMC	0.036
Carbopol 934	0.031
GMO 84	0.047
Polycarbophil	0.060

*: lamellar phase

3. <u>In vivo</u> test system for bioadhesion - washing off ability from the skin

A water soluble dye (Edicol Sunset Yellow, E 110, Amaranth E-123, or Brilliant Blue E 131) and/or a lipid soluble dye (Waxoline violet A FW (Maximex), Colur flavus insolubilis, DAK 63, or Edilake tartrazin NS) can be added to the test sample and mixed to form a homogeneous mixture. In those cases where a water soluble dye is used, the dye is preferably dissolved in an aqueous medium before mixing. In most cases, however, a dye is not added as the result is easily determined visually. About 0.05-0.5 g (such as 0.2 g) of the resulting mixture was applied in a uniform layer on an area of about 4 cm^2 of the skin of the hand or of the wrist. The test samples could be applied on dry skin as well as on moistened skin. In some cases, about 10 min before running the test, a small amount of water could be added to the test sample applied. Immediately after application, the test sample on the skin was subjected to washings with water from a tip (flow rate corresponding to about 6-8 litres/minute and a temperature of about 35-

40°C). The washings were carried out for about 3 minutes. Then it is visually assessed in which degree the test sample is retained on the skin. The visual assessment is done by use of a scale graded from 1-5, where 5 represents total retainment of the test sample applied on the skin and 1 represents no retainment of the test sample on the skin.

The test sample is evaluated to have bioadhesive properties in the present context if the result of the above-described test is at least 4.

The test described above has proved to be suitable when testing compositions for bioadhesiveness and the compositions in question have a relatively high viscosity which makes it difficult to apply the compositions to the rabbit jejunum model. A modification of the test described above excluding the addition of a water soluble dye has also proved suitable for testing compositions for bioadhesiveness.

Quantitative determinations of glycerylmonooleate and glycerylmonolinoleate by means of HPLC

The quantitative determination of glycerylmonooleate or glycerylmonolinoleate was made by high-performance liquid chromatography (HPLC) using a Shimadzu LC-6A HPLC pump, a Shimadzu SPD-6A UV detector, a Shimadzu C-5A integrator and a Shimadzu SIL-6B autosampler.

The column (25 cm x 4 mm i.d.) was packed with Supelcosil LC-18-DM and was eluted isocratically at ambient temperature with a mobile phase consisting of methanol:water:acetate buffer (pH 3.5) (840:120:40 v/v). However, in some cases interference from other substances may occur, and then it may be necessary to make minor changes in the composition of the eluent.

The size of a sample injected on the column was 20 µl and the flow rate was 1.2 ml/ml. The column effluent was monitored at 214 nm.

Extraction procedure prior to analysis of glycerylmonooleate or glycerylmonolinoleate in mucosa

The mucosa in question (with a second substance such as a fatty acid ester like e.g. glycerylmonooleate) is placed in 50.00 ml of methanol and shaken for 2 hours. The mixture is filtered through a 0.45 µm filter membrane (from Millipore 16555Q) and the filtrate is subjected to HPLC analysis using the method described above.

Recovery

In those cases where analysis is performed in order to determine the residual amount of the second substance such as the fatty acid ester like e.g. glycerylmonooleate on the rabbit jejunum segment in connection with the bioadhesive test No. 1 (above), the calculation of the residual amount takes into consideration an appropriate correction in the recovery. This correction is found based on determination of the amount of fatty acid ester on the rabbit jejunum segment after application of an accurate amount of the second substance (this test is repeated 5 times and the recovery is given as the mean value).

The recovery of about 125 mg GMO 84/ethanol 60/40% w/w on rabbit jejunum was examined. The recovery was found to be about 95%. The recovery was not determined for the other amounts of GMO/ethanol 60/40% w/w nor was it determined for GMO or GML formulations to which drug substances or excipients were added.

Solubility of acetylsalicylic acid (aspirin):

Wyatt D.M. and Dorschel O. A cubic phase delivery system composed of glyceryl monooleate and water for sustained release of water-soluble drugs, Pharm. Tech. 1992 (Oct.), p. 116-130, disclose an experiment in which aspirin is used. Aspirin is not a substance which has a low solubility in water at a pH prevailing in the composition such as appears from the following.

Aqueous solubility

The solubility of the weak acid aspirin is 3.3 mg/ml in water (20°C). It has a pKa value of about 3.5 (25°C) (Analytical Profiles). The solubility of aspirin is strongly dependent on the pH in the solution. The degree of ionisation of the acid group in aspirin is favoured when the pH is around and above the pKa value of the compound and therefore the solubility is increased with pH > 3.4. A solubility experiment has shown that the solubility of aspirin is greater than 10 mg/ml in a buffer solution of pH 3.6. The experiment was performed in an 0.5 M acetate buffer solution pH 4.0; the buffer was not strong enough to maintain the pH, and the pH in the final solution was 3.6. The solubility of aspirin in a buffer solution of pH 4.0 is > 20 mg/ml.

Solubility in GMO/water

The solubility of acetylsalicylic acid in GMO/water 65/35% w/w has been determined to be >20 mg/ml. During the experiment, the pH of the aqueous phase at the end of the experiment was

4.0 and the aqueous phase used was 0.2 M acetate buffer pH 5.0 (the buffer used was not strong enough to maintain the pH at 5.0)

Determination of the dissolution/release rate of a pharmaceutical formulation

The dissolution rate of acyclovir in various GMO compositions was determined using Franz diffusion cells having a diffusion area of 1.77 cm^2 and a receptor volume of 6.8 ml. The study was run at a temperature of 37°C and as diffusion membrane a cellulose membrane from Medicell International Ltd. was employed. The membrane employed has a pore size of about 2.4 nm and it retains particles having a molecular weight larger than about 12,000-14,000. Before application, the membrane was pretreated and thoroughly rinsed with distilled water. As receptor medium was used an isotonic 0.05M phosphate buffer pH 6.5 (Danish Drug Standards, DLS) and the medium was magnetically stirred at 100 rpm.

The cellulose membrane was allowed to equilibrate at 37°C for 30 min in the receptor medium employed. After placing the membrane in the diffusion cell (the membrane was supported by a metallic grating), about 300-400 mg of the composition to be tested was applied by means of a syringe or a spatula and care was taken to ensure a homogenous distribution of the composition on the total area of the membrane available for diffusion. Alternatively, the composition to be tested may be filled into a dish having a well-defined surface area which is only a little smaller than that of the cellulose membrane held by a Franz' diffusion cell so that almost all of the diffusion area available is used; the dish is turned upside down and placed on top of the cellulose membrane. Phosphate buffer was then loaded into the receptor part (time t=0) and at appropriate time intervals, samples of 2.0 ml were withdrawn and analyzed for content of acyclovir (cf. below). This relatively high volume was withdrawn to ensure sink condition. The amount of receptor medium withdrawn was replaced with fresh receptor medium.

Another well-suited dissolution test system for semi-solids is the Hanson p/n-S7-VC-IS-7 vertical diffusion cells (12 cells) from Hanson Research Corporation, U.S.A.

Quantitative determination of miconazole and lidocaine hydrochloride, respectively

Samples from Example 88 were analyzed for the content of miconazol and lidocain hydrochloride, respectively. The following assays were employed:

Lidocain HCl

The content of lidocain HCl is determined by a HPLC method.

T: Dissolve the formulation in 30 ml methanol and transfer it quantitatively to a 50 ml volumetric flask. Add methanol to 50.00 ml.

R: Weigh out 100.00 mg lidocain HCl in a 100 ml volumetric flask. Dilute 1000 µl to 50.00 ml with mobile phase.

Analyse T and R on a suitable liquid chromatograph with UV-detector and integrator.

Column:	Steel column, length 25 cm x 4.6 mm i.d.
Stationary phase:	Nucleosil C-18, 10 µm
Mobile phase:	Methanol R: Acetic acid: Triethylamine: Water (50:1.5:0.5:48)
Flow:	1.5 ml/min
Temperature:	Room temperature
Detection:	254 nm
Injection:	20 µl loop
Retention time:	Lidocain HCl: about 3 min

Calculation:

$$\text{Lidocain HCL recovery, \%:} \frac{A_T \times n(g)}{A_R \times m(g) \times \%\ \text{lidocain HCl}} \times 100\%$$

where
A_T is the area of the test solution T;
A_R is the area of the standard solution R;
n is the amount of standard weighed out (g);
m is the amount of formulation applied to the intestine (g);
% lidocain HCl is the content of lidocain HCl in the formulation determined as % w/w.

Miconazol

The content of miconazol is also determined by a HPLC method.

T: Dissolve the formulation in 30 ml methanol and transfer it quantitatively to a 50 ml volumetric flask. Add methanol to 50.00 ml.

R: Weigh out 100.00 mg miconazol in a 100 ml volumetric flask. Dilute 1000 µl to 50.00 ml with mobile phase.

Analyse T and R on a suitable liquid chromatograph with UV-detector and integrator.

Column:	Steel column, length 25 cm x 4.6 mm i.d.
Stationary phase:	Spherisorb ODS 1, S5
Mobile phase:	Methanol R: Buffer (85:15)
Flow:	1.0 ml/min
Temperature:	70°C
Detection:	230 nm
Injection:	20 µl loop
Retention time:	Miconazol: about 8 min
Buffer:	0.05 M $NH_4H_2PO_4$ (5.75 g in 1000 ml H_2O)

Calculation:

$$\text{Miconazol recovery, \%: } \frac{A_T \times n(g)}{A_R \times m(g) \times \%\ \text{miconazol}} \times 100\%$$

where A_T is the area of the test solution T;
A_R is the area of the standard solution R;
n is the amount of standard weighed out (g);
m is the amount of formulation applied to the intestine (g);
% miconazol is the content of miconazol in the formulation determined as % w/w.

Quantitative determination of acyclovir

Method A

Determination of acyclovir in aqueous media by HPLC

The HPLC method employed was the following:

Column:	25 cm x 4.6 mm i.d.
Stationary phase:	Nucleosil C-18
Mobile phase:	water:methanol (85:15)
Temperature:	Room temperature
Detection:	254 nm
Flow:	1 ml/min
Inj.volume:	20 µl
Ret. time:	ca. 5.4 min

In connection with dissolution/release rate experiments employing Franz diffusion cells as described above, the concentration in the test solution (C_n) is calculated as follows:

Reference solution: An accurate amount of about 10.00 mg acyclovir is diluted to with distilled water to a concentration of 10.00 µg/ml

Test solution: The sample withdrawn is filtered through a 0.2 µm filter and injected onto the column (in some cases it might be necessary to subject the sample to dilution with water)

$$C_n = \frac{A_T \text{ x amount weight in (mg) of reference x } 1000 \text{ x } 5}{A_R \text{ x } 100 \text{ x } 50} \ \mu g/ml$$

in which

A_T is the area of the test solution, and

A_R is the area of the reference solution.

Calculation of % released:

$$\frac{100 \text{ x } C_n \text{ x } V_t + (V_s \text{ x } \sum_{n=1}^{n} C_{n-1})}{\% \text{ of acyclovir in form. x mg of form. applied x } 1000} \text{ x } 100\%$$

in which

C_n is the concentration of drug in the receptor solution (mg/ml),

V_t is the receptor volume (unless otherwise stated, V_t = 6.8 ml),

V_s is the sample volume withdrawn,

C_{n-1} is the concentration in the previous sample (µg/ml).

Method B

Determination of acyclovir in pharmaceutical formulations by HPLC

The HPLC method employed was the following:

Column:	Steel column, 25 cm x 4.6 mm i.d.
Stationary phase:	Nucleosil C-18, 5 µm
Mobile phase:	water:methanol (20:80)
Temperature:	Room temperature
Detection:	254 nm
Flow:	0.8 ml/min
Inj.volume:	20 µl
Ret. time:	ca. 3.5 min

Reference solution: Weigh out an accurate amount of about 20.00 mg acyclovir and dilute it with mobile phase to a concentration of about 0.008 mg/ml

Test solution: Weight out 100.00 mg of the GMO/acyclovir formulation in a 50 ml volumetric flask. Dilute with mobile phase to 50.00 ml. Dilute 5.00 ml to 50.00 ml with mobile phase.

From the areas of the test solution and reference solution, respectively, the percentage of acyclovir present in the formulation is calculated.

Method C

Recovery of acyclovir on intestine

The HPLC method employed is the same as described under Method B. The test solution is prepared as follows:

The intestine is shaken for 2 hours with 50.00 ml of the mobile phase. The test solution is filtered through a 0.2 μm filter. Dilute 1000 μl to 10.00 ml with mobile phase.

From the areas of the test solution and reference solution, respectively, the percentage of acyclovir present in the formulation is calculated.

Determination of pH in the liquid crystalline phase

pH in the crystalline liquid phase is determined in a 10% w/w dispersion of the liquid crystalline phase (containing the active substance and any excipients) in distilled water. Prior to determination the dispersion is subjected to ultrasonic treatment for 30 minutes in order to ensure that an equilibrium between the liquid crystalline phase and the distilled water has taken place. The pH is measured by employment of a HAMILTON FLUSHTRODE which is a suitable pH-electrode for measurement of pH in the dispersions. The procedure followed was in accordance with the instructions given by the manufacturer of the electrode.

The method described above can be employed for various compositions, i.e. for composition wherein the concentration of the active ingredient in the liquid crystalline phase may be varied (e.g. from 1-20% w/w or in any range relevant for compositions according to the invention.

Modifications of the method described above may also be employed e.g. i) the dispersion mentioned above may obtained by diluting the liquid crystalline phase in a range corresponding to from about 1:20 to about 1:5 with distilled water, ii) ultrasonic treatment may be omitted or substituted by stirring or treatment in a rotomat provided that measures are taken to ensure that equilibrium takes place or, alternatively, that measurement of pH takes place after a well-defined time period, and iii) other suitable electrodes may be employed.

Most important is it to ensure that for comparative purposes the test conditions (stirring, ultrasonic treatment, time, electrodes) should be essentially the same when determining pH in the liquid crystalline phase of compositions.

In order to determine when an equilibrium between the liquid crystalline phase and the distilled water has taken place a number of experiments were performed varying the time period for ultrasonic treatment (0-5 hours) and measuring the pH immediate after the end of the ultra sonic treatment and 24 hours later. The experiments are performed on a GMO/water 65/35 containing 5% w/w of acyclovir. Based on the results of these experiments a time period of 30 minutes proved suitable, i.e. there is only an insignificant difference in the pH measured immediately after the end of ultra sonic treatment and 24 hours later.

Determination of drug solubility

The determination of the solubility of the active substance in the liquid crystalline phase of the composition is, of course, performed on the liquid crystalline phase as formed. In practice, this means that when the composition is one in which the liquid crystalline phase has already been formed when the composition is applied, the determination of the solubility is performed on the composition itself. The determination of the solubility is suitably performed by microscopy to observe any crystals of the active substance. Suitable test conditions involve a magnification of about 250 x and e.g. room temperature (20°C or 37°C may also be employed). The determination of the concentration at which crystals are observed is performed after a period of at least one week after preparation of the composition or the liquid crystalline phase to ensure that equilibrium has taken place. Normally, a series of tests with varying concentrations is performed to determine the concentration above which crystals are found. On the other hand, when the composition is a precursor composition, the liquid crystalline phase used as a reference in the solubility determination is a liquid crystalline phase imitating the liquid crystalline phase which will be formed when the composition absorbs liquid from the site of application. This reference liquid crystalline phase is made up with water (as representing the liquid absorbed) in such an amount that the reference liquid crystalline phase is the same type of liquid crystalline phase as is generated from the precursor composition.

In order to determine the aqueous solubility of the active substance at the pH prevailing in the liquid crystalline phase, the pH is determined in the liquid crystalline phase as described above to determine the pH conditions when determining the solubility. [Many experiments with GMO have revealed that the pH of the liquid crystalline phase predominantly is about 4.5, however, the pH depends on the quality of GMO employed.] The solubility of the active substance is then determined by stirring an excess amount of the active substance in water, where applicable, being buffered to a pH substantially identical to the pH prevailing in the liquid crystalline phase for a time period of at least 24 hours (to ensure that equilibrium has taken place) and at a constant temperature (e.g. 20°C, room temperature or 37°C). In some case the samples initially were subjected to ultrasonic treatment for half an hour in order to accelerate the time for equilibrium. The concentration of the active substance in the supernatant (i.e. the aqueous solubility at the given pH) is then determined by an appropriate assay (e.g. by HPLC or UV spectroscopy).

As mentioned above, when the pH of the liquid crystalline phase, determined as described herein, is different from the pH which will result simply by dissolution of the active substance in water, the water is adjusted to substantially the pH of the liquid crystalline phase by using a suitable buffer system when determining the solubility of the active substance. This buffer

system should of course be so selected that, apart from the pH adjustment, it has substantially no influence on the solubility of the active substance in the buffered water.

pH-solubility profile

Alternatively, the aqueous solubility is determined as a function of pH, i.e. by determining the aqueous solubility in buffer systems having a pH in a range of about 3 to about 9.5 such as about 3.6 to about 9. Suitable buffer systems include acetate, citrate, phosphate, borate etc. and the concentration of the buffer is sufficient to ensure a constant pH during the experiments. A concentration of at least 0.01 M is normally suitable. This method is applicable when determining the minimum aqueous solubility of a specific active substance at a given temperature and at a given pH range. The test conditions described (pH, temperature, ultrasonic treatment, stirring, time for ensuring that equilibrium has taken place) above are also valid when determining the minimum solubility.

Determination of liquid crystalline structure

Phase transitions of GMO 84 and/or GMO 90 containing compositions

In the following tests are described which make it possible to determine the crystalline structure of suitable compositions for use according to the invention. The tests allow determination of the presence of, e.g., the GMO 84 or GMO 90 in a lamellar, hexagonal or cubic phase, and it is possible to test the compositions before and after application to an appropriate application site. With respect to the various liquid crystalline phases formed by GMO or other glycerol fatty acid esters, an excellent review is given by Ericsson et al. in ACS Symp. Ser. (1991), pp 251-265, American Chemical Society and by Larsson in Chapter 8 (part 8.2.1 entitled "Lamellar and hexagonal liquid-crystalline phases") in The Lipids Handbook edited by Gunstone et al. In short, the lamellar phase is the dominating one at a relatively low water content (below 20% w/w) and at a temperature of about 37°C, whereas the cubic phase dominates as the water content increases (more than about 20% w/w).

A. Phase transition of GMO 84 and/or GMO 90 compositions determined by differential scanning calorimetry (DSC)

The DSC measurements were performed using a Perkin Elmer Unix DSC model 7 Differential Scanning Calorimeter. The heating rate was 5°C/min and the scanning temperature was from 5°C to 70°C. Samples were contained in sealed aluminium pans (Perkin Elmer No. BO14-3017) and as a reference empty aluminium pans were employed. The phase transitions caused only a

relatively small enthalpy change and, therefore, the amount of sample tested was optimized to about 30-40 mg. The prepared pans were sealed and stored for two days at 5°C prior to analysis.

B. Phase transition of GMO 84 and/or GMO 90 compositions determined by polarimetry

The liquid crystalline phase can also be determined using polarized light and e.g. employing a stereomicroscope (Leitz, Diaplane) equipped with polarization filters. The appearance of reversed micelles (L2) are seen as a liquid oil, the lamellar phase (L_α) is mucous-like and in polarized light it is birefringent. The appearance of the cubic phase is as a very viscous and glass-clear sample. In polarized light the cubic phase (Q) is optically isotropic and gives a black background with no details indicating that it does not reflect the light. The lamellar and hexagonal phases are optically anisotropic. The lamellar phase gives a structure like a pipe cleaner on a black background or, expressed in another manner, could be identified from the oily streak texture and the spherical, positive maltese cross-units visible between crossed polarisers. The reversed hexagonal phase gives different patterns but in most cases it resembles a mosaic-like structure or gives angular or fan-like textures.

The method can be employed in testing the phase behaviour of various bioadhesive compositions.

C. Phase transition of GMO 84 and/or GMO 90 compositions determined by X-ray diffraction

A modified diffraction thermal pattern (DTP) camera was employed. The source was an X-ray tube equipped with a Cu-anode emitting Kα-rays at a wavelength of 1.5418 Å. The X-ray generator was a Philips PW 1729.

The liquid crystalline state can be identified by low angle X-ray diffraction and its appearance in polarized light. The characteristic X-ray diffraction pattern for the three liquid crystalline phases (lamellar, hexagonal, cubic) will give rise to diffraction lines in the following orders:

$1:1/2:1/1:4$...(lamellar)
$1:1/\sqrt{3}:1/4:1/\sqrt{7}$...(hexagonal)
$1:1/\sqrt{2}:1/\sqrt{3}:1/\sqrt{4}:1/\sqrt{5}:1/\sqrt{6}:1/\sqrt{8}$...(cubic)

In the case of the cubic form, the 3 different lattices will give rise to three different diffraction lines.

EXAMPLES

The following examples 1-80 relate to the preparation and structure of compositions according to the invention.

Unless otherwise stated, all percentages are by weight.

In all examples, the glycerylmonooleate (abbreviated as GMO in the following) (and whenever relevant glycerylmonolinoleate (Dimodan® LS)) is gently melted on a heating plate or in an oven and the liquid obtained (max. temperature of the melted liquid is about 60°C) is cooled to about 40°C before mixing with other ingredients. The monoglyceride mixtures and the ingredients were mixed by stirring or shaking.

More specifically, compositions of GMO/Vitamin E TPGS, GMO/lecithin, and GMO/lecithin/Vitamin E TPGS, respectively, are prepared as follows:

GMO/Vitamin E TPGS:

GMO and Vitamin E TPGS are melted together at a temperature of max. 60°C. Alternatively, GMO and Vitamin E TPGS, respectively, are individually melted before mixing of the two components. Then the liquid phase is added.

GMO/lecithin:

Lecithin is dissolved in GMO at a temperature of about 60°C. Then the liquid phase is added. If the content of lecithin is >50% by weight of the GMO content (lecithin/GMO >0.5) then lecithin and the GMO may be dissolved in ether or ethanol followed by evaporation of the solvent by vacuum distillation. Then the liquid phase is added.

GMO/lecithin/Vitamin E TPGS:

Lecithin is dissolved in a GMO-Vitamin E TPGS phase at 60°C. The method described above involving ether or ethanol as solvent can also be employed.

GMO/lecithin/Vitamin E TPGS/acyclovir:

GMO and Vitamin E TPGS are melted at max. 60°C. Acyclovir is suspended into the melt under stirring. Epicuron 200 is dispersed in an aqueous medium by means of a homogenizer and is

then added to the GMO/Vitamin E TPGS/acyclovir mixture in a mortar under vigorous stirring until a homogeneous mixture is obtained. The mixture is subjected to ultrasonic treatment for 1 hour and left in an oven (37°C) for 2 days to ensure that equilibrium has taken place.

To the compositions described above any active drug substance and or other excipients are added or, alternatively, these substances are dissolved in the liquid phase before these two phases are mixed together.

In those cases where the composition contains an active substance in a GMO/ethanol or GML/ethanol vehicle or a lipid phase/ethanol vehicle, one of the following methods can be applied:

1. the active substance was dissolved or dispersed in ethanol and then mixed with melted GMO under stirring,
2. the active substance was dissolved or dispersed in melted GMO and then ethanol was added under stirring,
3. the active substance was dissolved or dispersed in a GMO/ethanol mixture.

When storing at room temperature (22°C) some formulations become inhomogeneous. In relevant cases the formulations were melted and stirred to obtain a homogeneous mixture before use.

An acyclovir ointment composition was prepared as follows:

In general, the acyclovir was suspended in the melted lipid phase and the other ingredients were added. The monoglyceride mixtures and the ingredients were mixed by stirring or shaking. The compositions were subjected to ultrasound treatment for about 1 h and were stored for at least two days at 37°C before use to ensure that equilibrium had been obtained (e.g. that the stable liquid crystalline phase has been formed in the total formulation and that equilibrium between the solid and dissolved substance has taken place). As an alternative to adding the acyclovir to the melted GMO, the acyclovir can be suspended in the liquid phase before combining the liquid phase with the melted GMO.

In those cases where a bioadhesive test is performed, the values given are mean values of the results of 2-4 tests. It should be noted that the values given in the Examples are not corrected for recovery, i.e. the values are minimum values. If a correction for recovery is made the values will become larger.

EXAMPLES 1-80

Ex.	Composition GMO-90/Epikuron 200/H_2O	Visual appearance at room temperature	Identification of liquid crystalline phase behaviour*
1	BGH 93: GMO-90/Epikuron 200/H_2O 60/10/30 % w/w	transparent, yellow, cubic consistency	black background, cubic
2	BGH 94: GMO-90/Epikuron 200/H_2O 50/20/30 % w/w	transparent, yellow, cubic consistency	black background, cubic
3	BGH 110: GMO-90/Epikuron200/H_2O 45/25/30 % w/w	Transparent, yellow	black background, cubic
4	BGH 95: GMO-90/Epikuron 200/H_2O 40/30/30 % w/w	cloudy, yellow, cubic consistency	black background, cubic
5	BGH 96: GMO-90/Epikuron 200/H_2O 30/40/30 % w/w	cloudy, yellow, softer than cubic consistency	non-cubic
6	BGH 97: GMO-90/Epikuron 200/H_2O 20/50/30 % w/w	cloudy, yellow, very soft	non-cubic
7	BGH 98: GMO-90/Epikuron 145/H_2O 60/10/30 % w/w	transparent, amber yellow, cubic consistency	black background, cubic
8	BGH 99: GMO-90/Epikuron 145/H_2O 50/20/30 % w/w	transparent, amber yellow, cubic consistency	cubic
9	BGH 100: GMO-90/Epikuron 45/H_2O 40/30/30 % w/w	cloudy, amber yellow, cubic consistency	non-cubic
10	BGH 101: GMO-90/Epikuron 45/H_2O 30/40/30 % w/w	cloudy, amber yellow, cubic consistency	non-cubic
11	BGH 102: GMO-90/Epikuron 45/H_2O 20/50/30 % w/w	cloudy, amber yellow, softer than cubic consistency	non-cubic
12	BGH 118: GMO-90/TPGS/H_2O 60/10/30 % w/w	transparent, cubic consistency	black background, cubic
13	BGH 119: GMO-90/TPGS/H_2O 50/20/30 % w/w	transparent, cubic consistency	black background, cubic
14	BGH 120: GMO-90/TPGS/H_2O 40/30/30 % w/w	cloudy, slightly yellow, much softer than cubic consistency (lamellar consistency)	non-cubic

Ex.	Composition GMO-90/Epikuron 200/H_2O	Visual appearance at room temperature	Identification of liquid crystalline phase behaviour*
15	BGH 121: GMO-90/TPGS/H_2O 30/40/30 % w/w	cloudy, slightly yellow, much softer than cubic consistency (lamellar consistency)	non-cubic
16	BGH 122: GMO-90/TPGS/H_2O 20/50/30 % w/w	cloudy, slightly yellow, much softer than cubic consistency (lamellar consistency)	non-cubic
17	BGH 123: GMO-90/Epikuron 200/H_2O + 5% TPGS 50/20/30 % w/w	transparent/cloudy, yellow, cubic consistency	black background, cubic
18	BGH 124: GMO-90/Epikuron 200/H_2O + 5% TPGS 50/20/30 % w/w	transparent/cloudy, yellow, cubic consistency	black background, cubic
19	BGH 126: GMO-90/Epikuron200/H_2O 43,7/24,3/32 % w/w	transparent, yellow, cubic consistency, excess water	black background, cubic
20	BGH 127: GMO-90/Epikuron200/H_2O 41,8/23,2/35 % w/w	transparent, yellow, cubic consistency, excess water	black background, cubic
21	BGH 128: GMO-90/Epikuron 200/H_2O 39,9/22,1/38 % w/w	transparent, yellow, cubic consistency, excess water	black background, cubic
22	BGH 125-1: GMO-90/Epikuron 200/H_2O 45/25/30 % w/w + 5% acyclovir (cryst)	cloudy, yellow, cubic consistency	black background, cubic, with close crystal structure
23	BGH 126-1: GMO-90/Epikuron 200/H_2O 43,7/24,3/32 % w/w + 5% acyclovir (cryst)	cloudy, yellow, cubic consistency, excess water	black background, cubic, with even and close crystal structure
24	BGH 127-1: GMO-90/Epikuron 200/H_2O 41,8/23,2/35 % w/w + 5% acyclovir (cryst)	cloudy, yellow, cubic consistency, disintegrates slightly, excess water	black background, cubic, with close crystal structure, little lumpy
25	BGH 128-1: GMO-90/Epikuron 200/H_2O 39,9/22,1/38 % w/w + 5% acyclovir (cryst)	cloudy, yellow, cubic consistency, excess water	black background, cubic, with close crystal structure, little lumpy
26	BGH 130: GMO-90/Epikuron 200/H_2O 38,9/29,1/32 % w/w	transparent, yellow, cubic consistency, ether smell	black background, cubic with grid structure

Ex.	Composition GMO-90/Epikuron 200/H_2O	Visual appearance at room temperature	Identification of liquid crystalline phase behaviour*
27	BGH 131: GMO-90/Epikuron 200/H_2O 37,1/27,9/35 % w/w	transparent, yellow, cubic consistency, ether smell	black background, cubic
28	BGH 132: GMO-90/Epikuron 200/H_2O 35,4/26,6/38 % w/w	transparent, yellow, cubic consistency, slightly disintegrates, ether smell	black background, cubic
29	BGH 129-1: GMO-90/Epikuron 200 /H_2O 40/30/30 % w/w + 5% acyclovir (cryst)	cloudy, yellow, cubic consistency, ether smell	black background, cubic with even and close crystal structure
30	BGH 130-1: GMO-90/Epikuron 200 /H_2O 38,9/29,1/32 % w/w + 5% acyclovir (cryst)	cloudy, yellow, cubic consistency, ether smell	black background, cubic with even and close crystal structure
31	BGH 131-1: GMO-90/Epikuron 200 /H_2O 37,1/27,9/35 % w/w + 5% acyclovir (cryst)	cloudy, yellow, cubic consistency, ether smell	black background, cubic, with close crystal structure, little lumpy
32	BGH 132-1: GMO-90/Epikuron 200 /H_2O 35,4/26,6/38 % w/w + 5% acyclovir (cryst)	cloudy, yellow, cubic consistency, ether smell	black background, cubic with even and close crystal structure
33	BGH 133: GMO-90/Epikuron 200 /H_2O/TPGS 38,3/21,3/25,5/15 % w/w (H_2O is added after 1 day with heat at 60 °C + stirring	transparent, cubic consistency	black background, cubic
34	BGH 134: GMO-90/Epikuron 200 /H_2O/TPGS 36/20/24/20 % w/w (H_2O is added after 1 day with heat at 60 °C + stirring	transparent, cubic consistency	black background, cubic
35	BGH 135: GMO-90/Epikuron 200 /H_2O/TPGS 35,5/19,7/29,8/15 % w/w (H_2O is added after 1 day with heat at 60 °C + stirring	transparent, cubic consistency	black background, cubic

Ex.	Composition GMO-90/Epikuron 200/H_2O	Visual appearance at room temperature	Identification of liquid crystalline phase behaviour*
36	BGH 136: GMO-90/Epikuron 200 /H_2O/TPGS 33,4/18,6/28/20 % w/w (H_2O is added after 1 day with heat at 60 °C + stirring	transparent, cubic consistency	black background, cubic
37	BGH 137: GMO-90/Epikuron 200 /H_2O/TPGS 34/25,5/25,5/15 % w/w (H_2O is added after 3 days with heat at 60 °C + stirring	cloudy/transparent, yellow, cubic consistency (cloudiness due to air)	black background, cubic
38	BGH 138: GMO-90/Epikuron 200 /H_2O/TPGS 32/24/24/20 % w/w (H_2O is added after 3 days with heat at 60 °C + stirring	cloudy/transparent, yellow, softer than cubic consistency (cloudiness due to air)	black background, cubic, plus something else
39	BGH 139: GMO-90/Epikuron 200 /H_2O/TPGS 31,5/23,7/29,8/15 % w/w (H_2O is added after 1 day with heat at 60 °C + stirring	cloudy/transparent, yellow, cubic consistency (cloudiness due to air)	black background, cubic
40	BGH 140: GMO-90/Epikuron 200 /H_2O/TPGS 29,7/22,3/28/20 % w/w (H_2O is added after 3 days with heat at 60 °C + stirring	cloudy, yellow, cubic consistency (cloudiness due to air)	black background, cubic, with H_{II} and $L\alpha$-patterns
41	BGH 133-1:GMO-90/Epikuron 200 /H_2O/TPGS 38,3/21,3/25,5/15 % w/w + 5% acyclovir (cryst) (H_2O is added after 1 day with heat at 60 °C + stirring	cloudy, yellow, cubic consistency	black background, cubic, with even and close crystal structure
42	BGH 134-1:GMO-90/Epikuron 200 /H_2O/TPGS 36/20/24/20 % w/w + 5% acyclovir (cryst) (H_2O is added after 1 day with heat at 60 °C + stirring	cloudy, yellow, cubic consistency	black background, cubic, with even and close crystal structure

Ex.	Composition GMO-90/Epikuron 200/H_2O	Visual appearance at room temperature	Identification of liquid crystalline phase behaviour*
43	BGH 135-1:GMO-90/Epikuron 200 /H_2O/TPGS 35,5/19,7/29,8/15 % w/w + 5% acyclovir (cryst) (H_2O is added after 1 day with heat at 60 °C + stirring	cloudy, yellow, cubic consistency	black background, cubic, with even and close crystal structure
44	BGH 136-1:GMO-90/Epikuron 200 /H_2O/TPGS 33,4/18,6/28/20 % w/w + 5% acyclovir (cryst) (H_2O is added after 1 day with heat at 60 °C + stirring	cloudy, yellow, cubic consistency, lumpy	black background, cubic, with even and close crystal structure
45	BGH 137-1:GMO-90/Epikuron 200 /H_2O/TPGS 34/25,5/25,5/15 % w/w + 5% acyclovir (cryst) (H_2O is added after 1 day with heat at 60 °C + stirring	cloudy, yellow, cubic consistency	black background, cubic, with even and close crystal structure and occasional lumps
46	BGH 138-1:GMO-90/Epikuron 200 /H_2O/TPGS 32/24/24/20 % w/w + 5% acyclovir (cryst) (H_2O is added after 3 days with heat at 60 °C + stirring	cloudy, yellow, cubic consistency, lumpy	black background, cubic, with even and close crystal structure
47	BGH 139-1:GMO-90/Epikuron 200 /H_2O/TPGS 31,5/23,7/29,8/15% w/w + 5% acyclovir (cryst) (H_2O is added after 1 day with heat at 60 °C + stirring	cloudy, yellow, cubic consistency	black background, cubic, with even and close crystal structure
48	BGH 140-1:GMO-90/Epikuron 200 /H_2O/TPGS 29,7/22,3/28/20% w/w + 5% acyclovir (cryst) (H_2O is added after 3 days with heat at 60 °C + stirring	cloudy, yellow, slightly softer than cubic consistency	black background, cubic, with even and close crystal structure
49	BGH 141: GMO-90/Epikuron 200/H_2O 47,9/19,1/33% w/w	transparent, yellow, slightly softer than cubic consistency (lump)	black background, cubic

Ex.	Composition GMO-90/Epikuron 200/H_2O	Visual appearance at room temperature	Identification of liquid crystalline phase behaviour*
50	BGH 142: GMO-90/Epikuron 200/H_2O 46,4/18,6/35% w/w	transparent, yellow, cubic consistency (lump)	black background, cubic
51	BGH 143: GMO-90/Epikuron 200/H_2O 44,3/17,7/38% w/w	transparent, yellow, cubic consistency (lump)	black background, cubic
52	BGH 141-1: GMO-90/Epikuron 200/H_2O 47,9/19,1/33% w/w + 5% acyclovir (cryst.)	cloudy, yellow, cubic consistency	black background, cubic, with even and close crystal structure
53	BGH 142-1: GMO-90/Epikuron 200/H_2O 46,4/18,6/35% w/w + 5% acyclovir (cryst.)	cloudy, yellow, cubic consistency, excess water	black background, cubic, with even and close crystal structure
54	BGH 143-1: GMO-90/Epikuron 200/H_2O 44,3/17,7/38% w/w + 5% acyclovir (cryst.)	cloudy, yellow, cubic consistency, excess liquid (lump)	black background, cubic, with even and close crystal structure
55	BGH 144: GMO-90/Epikuron 200/ H_2O/TPGS 45/18/27/10 % w/w	transparent, yellow, cubic consistency	black background, cubic
56	BGH 145: GMO-90/Epikuron 200/ H_2O/TPGS 41,8/16,7/31,5/10 % w/w	transparent, yellow, cubic consistency	black background, cubic
57	BGH 146: GMO-90/Epikuron 200/ H_2O/TPGS 42,5/17/25,5/15 % w/w	transparent, yellow, cubic consistency	black background, cubic
58	BGH 147: GMO-90/Epikuron 200/ H_2O/TPGS 39,4/15,8/29,8/15 % w/w	transparent, yellow, cubic consistency	black background, cubic
59	BGH 148: GMO-90/Epikuron 200/ H_2O/TPGS 40/16/24/20 % w/w	transparent, yellow, cubic consistency	black background, cubic
60	BGH 149: GMO-90/Epikuron 200/ H_2O/TPGS 37,1/14,9/28/20 % w/w	transparent, yellow, cubic consistency	black background, cubic
61	BGH 150: GMO-90/Epikuron 200/ H_2O/TPGS 37,1/20,7/27,2/15 % w/w	transparent, yellow, cubic consistency	black background, cubic

Ex.	Composition GMO-90/Epikuron 200/H_2O	Visual appearance at room temperature	Identification of liquid crystalline phase behaviour*
62	BGH 151: GMO-90/Epikuron 200/ H_2O/TPGS 33,9/18,8/32,3/15 % w/w	transparent, yellow, cubic consistency	black background, cubic
63	BGH 144-1: GMO-90/Epikuron 200/ H_2O/TPGS 45/18/27/10 % w/w + 5% acyclovir (cryst.)	cloudy, yellow, cubic consistency	black background, cubic, with even and close crystal structure
64	BGH 145-1: GMO-90/Epikuron 200/ H_2O/TPGS 41,8/16,7/31,5/10 % w/w + 5% acyclovir (cryst.)	cloudy, yellow, cubic consistency	black background, cubic, with even and close crystal structure
65	BGH 146-1: GMO-90/Epikuron 200/ H_2O/TPGS 42,5/17/25,5/15 % w/w + 5% acyclovir (cryst.)	cloudy, yellow, cubic consistency	black background, cubic, with even and close crystal structure
66	BGH 147-1: GMO-90/Epicuron 200/ H_2O/TPGS 39,4/15,8/29,8/15 % w/w + 5% acyclovir (cryst.)	cloudy, yellow, cubic consistency	black background, cubic, with even and close crystal structure
67	BGH 148-1: GMO-90/Epikuron 200/ H_2O/TPGS 40/16/24/20 % w/w + 5% acyclovir (cryst.)	cloudy, yellow, cubic consistency	black background, cubic, with even and close crystal structure
68	BGH 149-1: GMO-90/Epikuron 200/ H_2O/TPGS 37,1/14,9/28/20 % w/w + 5% acyclovir (cryst.)	cloudy, yellow, cubic consistency	black background, cubic, with even and close crystal structure
69	BGH 150-1: GMO-90/Epikuron 200/ H_2O/TPGS 37,1/20,7/27,2/15 % w/w + 5% acyclovir (cryst.)	cloudy, yellow, cubic consistency	black background, cubic, with even and close crystal structure
70	BGH 151-1: GMO-90/Epikuron 200/ H_2O/TPGS 33,9/18,8/32,3/15 % w/w + 5% acyclovir (cryst.)	cloudy, yellow, cubic consistency	black background, cubic, with even and close crystal structure
71	BGH 152: GMO-90/Epikuron 200/ H_2O/TPGS 35/19,4/25,6/20 % w/w	cloudy/transparent, yellow, cubic consistency	black background, cubic

Ex.	Composition GMO-90/Epikuron 200/H_2O	Visual appearance at room temperature	Identification of liquid crystalline phase behaviour*
72	BGH 153: GMO-90/Epikuron 200/ H_2O/TPGS 31,9/17,7/30,4/20 % w/w	cloudy/transparent, yellow, cubic consistency	black background, cubic,
73	BGH 154: GMO-90/TPGS/H_2O 55/15/30 % w/w	cloudy/transparent, grey, cubic consistency	black background, cubic
74	BGH 155: GMO-90/TPGS/H_2O 50/15/35 % w/w	cloudy/transparent, grey, cubic consistency	black background, cubic
75	BGH 156: GMO-90/TPGS/H_2O 45/20/35 % w/w	cloudy/transparent, grey, cubic consistency	black background, cubic,
76	BGH 152-1: GMO-90/Epikuron 200/ H_2O/TPGS 35/19,4/25,6/20 % w/w + 5% acyclovir (cryst.)	cloudy, yellow, cubic consistency (gritty)	black background, cubic, with even and close crystal structure
77	BGH 153-1: GMO-90/Epikuron 200/ H_2O/TPGS 31,9/17,7/30,4/20 % w/w + 5% acyclovir (cryst.)	cloudy, yellow, cubic consistency (gritty)	beginning $L\alpha$-lines with even and close crystal structure cubic with traces of lamellar phase
78	BGH 154-1: GMO-90/TPGS/H_2O 55/15/30 %w/w + 5% acyclovir (cryst.)	cloudy, whitish, cubic consistency	black background, cubic, with even and close crystal structure
79	BGH 155-1: GMO-90/TPGS/H_2O 50/15/35 %w/w + 5% acyclovir	cloudy, whitish, cubic consistency, lumps	black background, cubic, with even and close crystal structure
80	BGH 156-1: GMO-90/TPGS/H_2O 45/20/35 %w/w + 5% acyclovir	cloudy, whitish, cubic consistency, lumps	black background, cubic, with even and close crystal structure

EXAMPLE 81

Stability studies of compositions according to the invention

The purpose of the study is to examine the stability of compositions in which a cubic liquid crystalline phase has been generated and wherein structurants like Epikuron 200 and Vitamin E TPGS are included.

The compositions included in the study are left in transparent glass containers in a climate cabinet and the temperature is maintained at 15°C, 25°C or 40°C.

Samples are withdrawn at time t = 1 day after start of the experiment and at time t = 14 days and the samples are examined visually and by microscopy to investigate any change in the appearance of the compositions with respect to homogenicity, lipid precipitations, agglomerates of drug substance, etc. Presence of excess water and/or separation into two or more liquid phases are visual signs of instability and are therefore especially noted.

Each composition investigated is prepared using GMO-90 (with a content of GMO of about 90% w/w) or, alternatively, by using RYLO MG19 (with a content of about 90% GMO). The compositions which are prepared using both qualities of GMO have been marked with a * in the following.

The following studies are performed:

1. GMO/Vitamin E TPGS/water

Investigation of the influence of the concentration of vitamin E TPGS on the stability of the cubic liquid crystalline phase

Composition No.	GMO/Vitamin E TPGS/water composition
1	55/15/30
2	50/15/35
3	50/20/30
4*	46.4/18.6/35
5	55/15/30 + 5% w/w acyclovir
6	50/15/35 + 5% w/w acyclovir
7	50/20/30 + 5% w/w acyclovir
8*	46.4/18.6/35 + 5% w/w acyclovir

2. GMO/Epikuron 200/water

Investigation of the influence of the concentration of phophatidylcholine (Epikuron 200 is employed in this study) on the stability of the cubic liquid crystalline phase

Composition No.	GMO/Epikuron 200/water composition
9	50/20/30
10*	46.4/18.6/35
11	45/25/30
12	41.8/23.2/35
13(ether method)	40/30/30
14 (ether method)	37.1/27.9/35
15	50/20/30 + 5% w/w acyclovir
16*	46.4/18.6/35 + 5% w/w acyclovir
17	45/25/30 + 5% w/w acyclovir
18	41.8/23.2/35 + 5% w/w acyclovir
19 (ether method)	40/30/30 + 5% w/w acyclovir
20 (ether method)	37.1/27.9/35 + 5% w/w acyclovir

3. GMO/Epikuron 145 (about 45% phosphatidylcholine)/water

Investigation of the influence of the concentration of phophatidylcholine (Epikuron 145 is employed in this study) on the stability of the cubic liquid crystalline phase

Composition No.	GMO/Epikuron 145/water composition
21	46.4/18.6/35
22	46.4/18.6/35 + 5% w/w acyclovir

4. GMO/Epikuron 200/water/Vitamin E TPGS

Investigation of the influence of the concentration of phophatidylcholine (Epikuron 200 is employed in this study) and vitamin E TPGS on the stability of the cubic liquid crystalline phase

Composition No.	GMO/Epikuron 200/water/Vitamin E TPGS composition
23	45/18/27/10 = 50/20/30 + 10% w/w TPGS
24	41.8/16.7/31.5/10 = 46.4/18.6/35 + 10% w/w TPGS
25	42.5/17/25.5/15 = 50/20/30 + 15% w/w TPGS

26	41.3/16.5/27.2/15 = 48.6/19.4/32 + 15% w/w TPGS
27*	39.4/15.8/29.8/15 = 46.4/18.6/35 + 15% w/w TPGS
28	37.7/15/32.3/15 = 44.3/17.7/38 + 15% w/w TPGS
29	40/16/24/20 = 50/20/30 + 20% w/w TPGS
30*	37.1/14.9/28/20 = 46.4/18.6/35 + 20% w/w TPGS
31	34.3/13.7/32/20 = 42.9/17.1/40 + 20% w/w TPGS
32	38.3/21.3/25.5/15 =45/25/30 + 15% w/w TPGS
33	35.5/19.7/29.8/15 =41.8/23.2/35 + 15% w/w TPGS
34	36/20/24/20 = 45/25/30 + 20% w/w TPGS
35	33.4/18.6/28/20 = 41.8/23.2/35 + 20% w/w TPGS
36	45/18/27/10 = (50/20/30 + 10% w/w TPGS) + 5% w/w acyclovir
37	41.8/16.7/31.5/10 = (46.4/18.6/35 + 10% w/w TPGS) + 5% w/w acyclovir
38	42.5/17/25.5/15 = (50/20/30 + 15% w/w TPGS) + 5% w/w acyclovir
39	41.3/16.5/27.2/15 = (48.6/19.4/32 + 15% w/w TPGS) + 5% w/w acyclovir
40*	39.4/15.8/29.8/15 = (46.4/18.6/35 + 15% w/w TPGS) + 5% acyclovir
41	37.7/15/32.3/15 = (44.3/17.7/38 + 15% TPGS) + 5% w/w acyclovir
42	40/16/24/20 = (50/20/30 + 20% w/w TPGS) + 5% w/w acyclovir
43*	37.1/14.9/28/20 = (46.4/18.6/35 + 20% w/w TPGS) + 5% w/w acyclovir
44	34.3/13.7/32/20 = (42.9/17.1/40 + 20% w/w TPGS) + 5% w/w acyclovir
45	38.3/21.3/25.5/15 = (45/25/30 + 15% w/w TPGS) + 5% w/w acyclovir

46	35.5/19.7/29.8/15 = (41.8/23.2/35 + 15% w/w TPGS) + 5% w/w acyclovir
47	36/20/24/20 = (45/25/30 + 20% w/w TPGS) + 5% w/w acyclovir
48	33.4/18.6/28/20 = (41.8/23.2/35 + 20% w/w TPGS) + 5% w/w acyclovir

Results: The stability studies showed that all the compositions tested were stable for at least 1 month at 15°C, 25°C and 40°C at a relative humidity according to the accepted guidelines. In polarized light it was observed that a cubic liquid crystalline phase was still present in all compositions tested.

5. GMO/Epikuron 145/water/Vitamin E TPGS (% w/w)

Investigation of the influence of the concentration of lecithin (Epikuron 145 is employed in this study) and vitamin E TPGS on the stability of the cubic liquid crystalline phase

Composition No.	GMO/Epikuron 145/water/Vitamin E TPGS composition
49	39.4/15.8/29.8/15 = 46.4/18.6/35 + 15% w/w TPGS
50	39.4/15.8/29.8/15 = (46.4/18.6/35 + 15% w/w TPGS) + 5% w/w acyclovir
51	37.1/14.9/28/20 = 46.4/18.6/35 + 20% w/w TPGS
52	37.1/14.9/28/20 = (46.4/18.6/35 + 20% w/w TPGS) + 5% w/w acyclovir

6. Stability at 25°C and 60% relative humidity

In the following stability tests, the liquid crystalline phase was investigated by means of polarised light at 22°C. The compositions investigated was prepared by dissolving Epikuron 200 in melted GMO/Vitamin E TPGS (max. 60°C).

Batch no.	Formulation	Months	Appearance (22°C)	Phase description*
BGH 178	GMO90/epicuron200/TPGS/water 41,8/16,7/10/31,5	0	clear yellow, cubic consistency	cubic
		0.5		
		1.5	clear - yellow, cubic consistency	cubic
		3	clear - yellow, cubic consistency	cubic
		8.5	clear yellow, cubic consistency	cubic
BGH 179	GMO90/epicuron200/TPGS/water 42,5/17/15/25,5	0	clear yellow, cubic consistency	cubic
		0.5		
		1.5	clear yellow, cubic consistency	cubic
		3	clear yellow, cubic consistency	cubic
		8.5	clear yellow, cubic consistency	cubic
BGH 180	GMO90/epicuron200/TPGS/water 41,3/16,5/15/27,2	0	clear yellow, cubic consistency	cubic
		0.5		
		1.5	clear yellow, cubic consistency	cubic
		3	clear yellow, cubic consistency	cubic
		8.5	clear yellow, cubic consistency	cubic

BGH 181	GMO90/epicuron200/TPGS/water 39,4/15,8/15/29.8	0	clear yellow, cubic consistency	cubic
		0.5		
		1.5	clear yellow, cubic consistency	cubic
		3	clear yellow, cubic consistency	cubic
		8.5	clear yellow, cubic consistency	cubic
BGH 182	GMO90/epicuron200/TPGS/water 37,7/15/15/32,3	0	clear yellow, cubic consistency	cubic
		0.5		
		1.5	clear yellow, cubic consistency	cubic
		3	clear yellow, cubic consistency	cubic
		8,5	clear yellow, cubic consistency	cubic
BGH 186	GMO90/epicuron200/TPGS/water 38,3/21.3/15/25,5	0	clear yellow, cubic consistency	cubic
		0.5		
		1.5	clear yellow, cubic consistency	cubic
		3	clear yellow, cubic consistency	cubic
		8,5	yellow, a little unclear, cubic consistency	cubic
BGH 187	GMO90/epicuron200/TPGS/water 35.5/19,7/15/29,8	0	clear yellow, cubic consistency	cubic
		0.5		
		1.5	clear yellow, cubic consistency	cubic
		3	clear yellow, cubic consistency	cubic
		8,5	clear yellow, cubic consistency	cubic

BGH 188	GMO90/epicuron200/TPGS/water 36/20/20/24	0	clear yellow, cubic consistency	cubic
		0.5		
		1.5	clear yellow, cubic consistency	cubic
		3	clear yellow, cubic consistency	cubic
		8,5	clear yellow, cubic consistency	cubic
BGH 189	GMO90/epicuron200/TPGS/water 33,4/18,6/20/28	0	clear yellow, cubic consistency	cubic
		0.5		
		1.5	clear yellow, cubic consistency	cubic
		3	clear yellow, cubic consistency	cubic
		8,5	clear yellow, cubic consistency	cubic

Stability of various GMO/PC/TPGS/water formulations added 5% w/w acyclovir (AC) at 25°C/60%RH.

Batch no.	Formulation	Months	appearance	Phase description
BGH 191	GMO90/epicuron200/TPGS/water 41,8/16,7/10/31,5 + 5% AC	0	unclear yellow, cubic consistency	cubic
		0.5	unclear yellow, cubic consistency	cubic
		1.5	white-yellow, cubic consistency	cubic
		3	unclear yellow, cubic consistency	cubic
		8,5	yellow, softer than cubic consistency	
BGH 192	GMO90/epicuron200/TPGS/water 42,5/17/25,5/15 + 5% AC	0	unclear yellow, cubic consistency	cubic
		0.5	unclear yellow, cubic consistency	cubic
		1.5	white-yellow, cubic consistency	cubic
		3	unclear yellow, cubic consistency	cubic
		8,5	yellow, cubic consistency	cubic
BGH 193	GMO90/epicuron200/TPGS/water 41,3/16,5/15/27,2 + 5% AC	0	unclear yellow, cubic consistency	cubic
		0.5	unclear yellow, cubic consistency	cubic
		1.5	white-yellow, cubic consistency	cubic
		3	unclear yellow, cubic consistency	cubic
		8,5	yellow, cubic consistency	cubic
BGH 196	GMO90/epicuron200/TPGS/water 40/16/20/24 + 5% AC	0	unclear yellow, cubic consistency	cubic
		0.5	unclear yellow, cubic consistency	cubic
		1.5	white-yellow, cubic consistency	cubic
		3	unclear yellow, cubic consistency	cubic
		8,5	yellow, cubic consistency	cubic

BGH 197	GMO90/epicuron200/TP GS/water 37,1/14,9/20/28 + 5% AC	0	unclear yellow, cubic consistency	cubic
		0.5	unclear yellow, cubic consistency	cubic
		1.5	white-yellow, cubic consistency	cubic
		3	unclear yellow, cubic consistency	cubic
		8,5	yellow, cubic consistency	cubic
BGH 198	GMO90/epicuron200/TP GS/water 34,3/13,7/20/32 + 5% AC	0	unclear yellow, cubic consistency	cubic
		0.5	unclear yellow, cubic consistency	cubic
		1.5	white-yellow, cubic consistency	cubic
		3	unclear yellow, cubic consistency	cubic
		8,5	yellow, cubic consistency	cubic
BGH 199	GMO90/epicuron200/TP GS/water 38,3/21,3/15/25,5 + 5% AC	0	unclear yellow, cubic consistency	cubic
		0.5	unclear yellow, cubic consistency	cubic
		1.5	white-yellow, cubic consistency	cubic
		3	unclear yellow, cubic consistency	cubic
		8,5	yellow, cubic consistency	cubic
BGH 200	GMO90/epicuron200/TP GS/water 35,5/19,7/15/29,8 + 5% AC	0	unclear yellow, cubic consistency	cubic
		0.5	unclear yellow, cubic consistency	cubic
		1.5	white-yellow, cubic consistency	cubic
		3	unclear yellow, cubic consistency	cubic
		8,5	yellow, cubic consistency	cubic

BGH 201	GMO90/epicuron200/TP GS/water 36/20/20/24 + 5% AC	0	unclear yellow, cubic consistency	cubic
		0.5	unclear yellow, cubic consistency	cubic
		1.5	white-yellow, cubic consistency	cubic
		3	unclear yellow, cubic consistency	cubic
		8,5	yellow, cubic consistency	cubic
BGH 202	GMO90/epicuron200/TP GS/water 33,4/18,6/20/28 + 5% AC	0	unclear yellow, cubic consistency	cubic
		0.5	unclear yellow, cubic consistency	cubic
		1.5	unclear yellow, cubic consistency	cubic
		3	unclear yellow, cubic consistency	cubic
		8,5	yellow, cubic consistency	cubic

Batch no.	Formulation	Months	Appearance (22°C)	Phase description*
BGH 157	GMO90/TPGS/water	0	clear to week grey, cubic consistency	cubic
	55/15/30	0.75	clear to week grey, cubic consistency	cubic
		1.5		
		3	clear to week grey, cubic consistency	cubic
		9	clear brownish, cubic consistency	cubic
BGH 158	GMO90/TPGS/water	0	clear to week grey, cubic consistency	cubic
	50/15/35	0.75	clear to week grey, cubic consistency	cubic
		1.5		
		3	clear to week grey, cubic consistency	cubic
		9	clear brownish , cubic consistency	cubic
BGH 159	GMO90/TPGS/water	0	clear to week grey, cubic consistency	cubic
	50/20/30	0.75	Clear to week grey, cubic consistency	cubic
		1.5		
		3	clear to week grey, cubic consistency	cubic
		9	clear marbled discoloured , cubic consistency	cubic
BGH 160	GMO90/TPGS/water	0	clear to week grey, cubic consistency	cubic
	46.4/18,6/35	0.75	clear to week grey, cubic consistency	cubic
		1.5		
		3	clear to week grey, cubic consistency	cubic
		9	clear marbled discoloured , cubic consistency	cubic
BGH 161	GMO90/TPGS/water 55/15/30 + 5% AC	0	white-unclear, cubic consistency	cubic
		0.75	white-unclear, cubic consistency	cubic
		1.5		
		3	white-unclear, cubic consistency	cubic
		9	white, cubic consistency	cubic

BGH 162	GMO90/TPGS/water 50/15/35 + 5% AC	0	white-unclear, cubic consistency	cubic
		0.75	white-unclear, cubic consistency	cubic
		1.5		
		3	white-unclear, cubic consistency	cubic
BGH 163	GMO90/TPGS/water 50/20/30 + 5% AC	0	white-unclear, cubic consistency	cubic
		0.75	white-unclear, cubic consistency	cubic
		1.5		
		3	white-unclear, cubic consistency	cubic
		9	white, cubic consistency	cubic

7. Stability at 40°C and 75% relative humidity

In the following stability tests, the liquid crystalline phase was investigated by means of polarised light at 22°C. The compositions investigated was prepared by dissolving Epikuron 200 in melted GMO/Vitamin E TPGS (max. 60°C).

Batch no.	Formulation	Months	Appearance (22°C)	Phase description*
BGH 178	GMO90/epicuron200/TPGS/water 41,8/16,7/10/31,5	0	clear yellow, cubic consistency	cubic
		0.5		
		1.5	clear yellow, cubic consistency	cubic
		3		
		8.5	fluid	unstable
BGH 179	GMO90/epicuron200/TPGS/water 42,5/17/15/25,5	0	clear yellow, cubic consistency	cubic
		0.5		
		1.5	clear yellow, cubic consistency	cubic
		3		
		8.5	fluid	unstable
BGH 180	GMO90/epicuron200/TPGS/water 41,3/16,5/15/27,2	0	clear yellow, cubic consistency	cubic
		0.5		
		1.5	clear yellow, cubic consistency	cubic
		3		
		8.5	fluid	unstable
BGH 181	GMO90/epicuron200/TPGS/water 39,4/15,8/15/29.8	0	clear yellow, cubic consistency	cubic
		0.5		
		1.5	clear yellow, cubic consistency	cubic
		3		
		8.5	fluid	unstable

BGH 182	GMO90/epicuron200/TPGS/water 37,7/15/15/32,3	0	clear yellow, cubic consistency	cubic
		0.5		
		1.5	clear yellow, cubic consistency	cubic
		3		
		8,5	fluid	unstable
BGH 186	GMO90/epicuron200/TPGS/water 38,3/21.3/15/25,5	0	clear yellow, cubic consistency	cubic
		0.5		
		1.5	clear yellow, cubic consistency	cubic
		3		
		8,5	fluid	unstable
BGH 187	GMO90/epicuron200/TPGS/water 35.5/19,7/15/29,8	0	clear yellow, cubic consistency	cubic
		0.5		
		1.5	clear yellow, cubic consistency	cubic
		3		
		8,5	fluid	unstable
BGH 188	GMO90/epicuron200/TPGS/water 36/20/20/24	0	clear yellow, cubic consistency	cubic
		0.5		
		1.5	clear yellow, cubic consistency	cubic
		3		
		8,5	unclear yellow, excess water, softer than cubic consistency	rev. hexagonal
BGH 189	GMO90/epicuron200/TPGS/water 33,4/18,6/20/28	0	clear yellow, cubic consistency	cubic
		0.5		
		1.5	clear yellow, cubic consistency	cubic
		3		
		8,5	unclear yellow, excess water, softer than cubic consistency	rev. hexagonal

GMO/PC/TPGS/Water formulations containing 5% w/w % acyclovir

Batch no.	Formulation	Months	Appearance (22°C)	Phase description*
BGH 191	GMO90/epicuron200/TPGS/water	0	unclear yellow, cubic consistency	cubic
	41,8/16,7/10/31,5	0.5	unclear yellow, cubic consistency	cubic
	+ 5% AC	1.5	white-yellow, cubic consistency	cubic
BGH 192	GMO90/epicuron200/TPGS/water	0	unclear yellow, cubic consistency	cubic
	42,5/17/15/25,5	0.5	unclear yellow, cubic consistency	cubic
	+ 5% AC	1.5	white-yellow, cubic consistency	cubic
		3		
		9	pale yellow, softer than cubic consistency	rev. hexagonal
BGH 193	GMO90/epicuron200/TPGS/water	0	unclear yellow, cubic consistency	cubic
	41,3/16,5/15/27,2	0.5	unclear yellow, cubic consistency	cubic
	+ 5% AC	1.5	white-yellow, cubic consistency	cubic
		3		
		9	pale yellow, softer than cubic consistency	rev. hexagonal
BGH 194	GMO90/epicuron200/TPGS/water	0	unclear yellow, softer than cubic consistency	traces of something else than the cubic phase
	39,4/15.8/29,8/15	0.5	unclear yellow, softer than cubic consistency	phase change
	+ 5% AC	1.5	two phase system, fluid	unstable
		3		
		9	fluid	unstable

BGH 196	GMO90/epicuron200/TPGS/water 40/16/20/24 + 5% AC	0	unclear yellow, cubic consistency	cubic
		0.5	unclear yellow, cubic consistency	cubic
		1.5	white-yellow, cubic consistency	cubic
		3		
		9	pale yellow, softer than cubic consistency	rev. hexagonal
BGH 197	GMO90/epicuron200/TPGS/water 37,1/14,9/20/28 + 5% AC	0	unclear yellow, cubic consistency	cubic
		0.5	unclear yellow, cubic consistency	cubic
		1.5	white-yellow, cubic consistency	cubic
		3		
		9	pale yellow, softer than cubic consistency	rev. hexagonal
BGH 198	GMO90/epicuron200/TPGS/water 34,3/13,7/20/32 + 5% AC	0	unclear yellow, cubic consistency	cubic
		0.5	unclear yellow, cubic consistency	cubic
		1.5	white-yellow, cubic consistency	cubic
		3		
		9	pale yellow, softer than cubic consistency	rev. hexagonal
BGH 199	GMO90/epicuron200/TPGS/water 38,3/21,3/15/25,5 + 5% AC	0	unclear yellow, cubic consistency	cubic
		0.5	unclear yellow, cubic consistency	cubic
		1.5	white-yellow, cubic consistency	cubic
		3		
		9	fluid	unstable
BGH 200	GMO90/epicuron200/TPGS/water 35,5/19,7/15/29,8 + 5% AC	0	unclear yellow, cubic consistency	cubic
		0.5	unclear yellow, cubic consistency	cubic
		1.5	white-yellow, cubic consistency	cubic
		3		
		9	fluid	unstable

BGH 201	GMO90/epicuron200/TPGS/water 36/20/20/24 + 5% AC	0	unclear yellow, cubic consistency	cubic
		0.5	unclear yellow, cubic consistency	cubic
		1.5	white-yellow, cubic consistency	cubic
		3		
		9	fluid	unstable
BGH 202	GMO90/epicuron200/TPGS/water 33,4/18,6/20/28 + 5% AC	0	unclear yellow, cubic consistency	cubic
		0.5	unclear yellow, cubic consistency	cubic
		1.5	unclear yellow, cubic consistency	cubic
		3		
		9	pale yellow with few dark yellow spots, separates, softer than cubic consistency	rev. hexagonal

Batch no.	Formulation	Months	Appearance (22°C)	Phase discription*
BGH 157	GMO90/TPGS/water 55/15/30	0	clear to week grey, cubic consistency	cubic
		0.75	clear to week grey, cubic consistency	cubic
		1.5		
		3		
		8.5	unclear brownish , cubic consistency	rev. hexagonal
BGH 158	GMO90/TPGS/water 50/15/35	0	clear to week grey, cubic consistency	cubic
		0.75	Clear to week grey, cubic consistency	cubic
		1.5		
		3		
		8.5	unclear brownish , cubic consistency	rev. hexagonal
BGH 159	GMO90/TPGS/water 50/20/30	0	clear to week grey, cubic consistency	cubic
		0.75	clear to week grey, cubic consistency	cubic
		1.5		
		3		
		8.5	clear marbled discoloured , cubic consistency	cubic
BGH 160	GMO90/TPGS/water 46.4/18,6/35	0	clear to week grey, cubic consistency	cubic
		0.75	clear to week grey, cubic consistency	cubic
		1.5		
		3		
		8.5	clear marbled discoloured , cubic consistency	cubic
BGH 161	GMO90/TPGS/water 55/15/30 + 5% AC	0	white-unclear, cubic consistency	cubic
		0.75	white-unclear, cubic consistency	cubic
		1.5		
		3		
		8.5	white, cubic consistency	cubic
BGH 162	GMO90/TPGS/water 50/15/35 + 5% AC	0	white-unclear, cubic consistency	cubic
		0.75	white-unclear, cubic consistency	cubic
		1.5		
		3		
		8,5	white, cubic consistency	cubic
BGH 163	GMO90/TPGS/water 50/20/30 + 5% AC	0	white-unclear, cubic consistency	cubic
		0.75	white-unclear, cubic consistency	cubic
		1.5		
		3	white-unclear, cubic consistency	cubic
		8,5	white, cubic consistency	cubic
BGH 164	GMO90/TPGS/water 46,4/18,6/35 + 5% AC	0	white-unclear, cubic consistency	cubic
		0.75	white-unclear, cubic consistency	cubic
		1.5		
		3		
		8,5	white, cubic consistency	cubic

8. Stability at 15°C (cooling cabinet)
Method: polarized light at 22°C

Batch no.	Formulation	Months	Appearance (22°C)	Phase description*
BGH 157	GMO90/TPGS/water 55/15/30	0	clear to week grey, cubic consistency	cubic
		0.75	clear to week grey, cubic consistency	cubic
		1.5		
		3	clear to week grey, cubic consistency	cubic
		9	clear to week grey, cubic consistency	cubic
BGH 158	GMO90/TPGS/water 50/15/35	0	clear to week grey, cubic consistency	cubic
		0.75	Clear to week grey, cubic consistency	cubic
		1.5		
		3	clear to week grey, cubic consistency	cubic
		8.5	clear to week grey, cubic consistency	cubic
BGH 159	GMO90/TPGS/water 50/20/30	0	clear to week grey, cubic consistency	cubic
		0.75	clear to week grey, cubic consistency	cubic
		1.5		
		3	clear to week grey, cubic consistency	cubic
		8.5	clear to week grey, cubic consistency	cubic
BGH 160	GMO90/TPGS/water 46.4/18,6/35	0	clear to week grey, cubic consistency	cubic
		0.75	clear to week grey, cubic consistency	cubic
		1.5		
		3	clear to week grey, cubic consistency	cubic
		8.5	clear to week grey, cubic consistency	cubic
BGH 161	GMO90/TPGS/ water 55/15/30 + 5% AC	0	white-unclear, cubic consistency	cubic
		0.75	white-unclear, cubic consistency	cubic
		1.5		
		3	white-unclear, cubic consistency	cubic
		8.5	yellow-brown, cubic consistency	cubic
BGH 162	GMO90/TPGS/ water 50/15/35 + 5% AC	0	white-unclear, cubic consistency	cubic
		0.75	white-unclear, cubic consistency	cubic
		1.5		
		3	white-unclear, cubic consistency	cubic
		8,5	white, softer than cubic consistency	phase change

BGH 163	GMO90/TPGS/ water 50/20/30 + 5% AC	0	white-unclear, cubic consistency	cubic
		0.75	white-unclear, cubic consistency	cubic
		1.5		
		3	white-unclear, cubic consistency	cubic
		8,5	white, softer than cubic consistency	phase change

Batch no.	Formulation	Months	Appearance (22°C)	Phase description*
BGH 178	GMO90/epicuron200/TPGS/ water 41,8/16,7/10/31,5	0	clear yellow, cubic consistency	cubic
		0.5		
		1.5	clear yellow, cubic consistency	cubic
		3	clear yellow, cubic consistency	cubic
		9	clear yellow, cubic consistency	cubic
BGH 179	GMO90/epicuron200/TPGS/ water 42,5/17/15/25,5	0	clear yellow, cubic consistency	cubic
		0.5		
		1.5	clear yellow, cubic consistency	cubic
		3	clear yellow, cubic consistency	cubic
		9	clear yellow, cubic consistency	cubic
BGH 180	GMO90/epicuron200/TPGS/ water 41,3/16,5/15/27,2	0	clear yellow, cubic consistency	cubic
		0.5		
		1.5	clear yellow, cubic consistency	cubic
		3	clear yellow, cubic consistency	cubic
		9	clear yellow, cubic consistency	cubic
BGH 181	GMO90/epicuron200/TPGS/ water 39,4/15,8/15/29.8	0	clear yellow, cubic consistency	cubic
		0.5		
		1.5	clear yellow, cubic consistency	cubic
		3	clear yellow, cubic consistency	cubic
		9	clear yellow, cubic consistency	cubic
BGH 182	GMO90/epicuron200/TPGS/ water 37,7/15/15/32,3	0	clear yellow, cubic consistency	cubic
		0.5		
		1.5	clear yellow, cubic consistency	cubic
		3	clear yellow, cubic consistency	cubic
		9	clear yellow, cubic consistency	cubic
BGH 184	GMO90/epicuron200/TPGS/ water 37,1/14,9/20/28	0	clear yellow, cubic consistency	cubic
		0.5		
		1.5	clear yellow, cubic consistency	cubic
		3	clear yellow, cubic consistency	cubic
		9	clear yellow, cubic consistency	cubic
BGH 186	GMO90/epicuron200/TPGS/ water 38,3/21.3/15/25,5	0	clear yellow, cubic consistency	cubic
		0.5		
		1.5	clear yellow, cubic consistency	cubic
		3	clear yellow, cubic consistency	cubic
		9	clear yellow, cubic consistency	cubic
BGH 187	GMO90/epicuron200/TPGS/ water 35.5/19,7/15/29,8	0	clear yellow, cubic consistency	cubic
		0.5		
		1.5	clear yellow, cubic consistency	cubic
		3	clear yellow, cubic consistency	cubic
		9	clear yellow, cubic consistency	cubic
BGH 188	GMO90/epicuron200/TPGS /water 36/20/20/24	0	clear yellow, cubic consistency	cubic
		0.5		
		1.5	clear yellow, cubic consistency	cubic
		3	clear yellow, cubic consistency	cubic
		9	clear yellow, cubic consistency	cubic

BGH 189	GMO90/epicuron200/TPGS /water 33,4/18,6/20/28	0	clear yellow, cubic consistency	cubic
		0.5		
		1.5	clear yellow, cubic consistency	cubic
		3	clear yellow, cubic consistency	cubic
		9	unclear yellow, softer than cubic consistency	phase change

GMO/PC/TPGS/Water formulations containing 5% w/w % acyclovir
15°C cooling cabinet

Batch no.	Formulation	Months	Appearance (22°C)	Phase description*
BGH 191	GMO90/epicuron200/TPGS /water 41,8/16,7/10/31,5 + 5% AC	0	unclear yellow, cubic consistency	cubic
		0.5	unclear yellow, cubic consistency	cubic
		1.5		
		3	unclear yellow, cubic consistency	cubic
		9	unclear yellow, cubic consistency	cubic
BGH 192	GMO90/epicuron200/TPGS /water 42,5/17/15/25,5 + 5% AC	0	unclear yellow, cubic consistency	cubic
		0.5	unclear yellow, cubic consistency	cubic
		1.5		
		3	unclear yellow, cubic consistency	cubic
		9	unclear yellow, cubic consistency	cubic
BGH 193	GMO90/epicuron200/TPGS /water 41,3/16,5/15/27,2 + 5% AC	0	unclear yellow, cubic consistency	cubic
		0.5	unclear yellow, cubic consistency	cubic
		1.5		
		3	unclear yellow, cubic consistency	cubic
		9	unclear yellow, cubic consistency	cubic
BGH 196	GMO90/epicuron200/TPGS /water 40/16/20/24 + 5% AC	0	unclear yellow, cubic consistency	cubic
		0.5	unclear yellow, cubic consistency	cubic
		1.5		
		3	unclear yellow, cubic consistency	cubic
		9	unclear yellow, cubic consistency	cubic
BGH 197	GMO90/epicuron200/TPGS /water 37,1/14,9/20/28 + 5% AC	0	unclear yellow, cubic consistency	cubic
		0.5	unclear yellow, cubic consistency	cubic
		1.5		
		3	unclear yellow, cubic consistency	cubic
		9	unclear yellow, cubic consistency	cubic
BGH 198	GMO90/epicuron200/TPGS /water 34,3/13,7/20/32 + 5% AC	0	unclear yellow, cubic consistency	cubic
		0.5	unclear yellow, cubic consistency	cubic
		1.5		
		3	unclear yellow, cubic consistency	cubic
		9	unclear yellow, cubic consistency	cubic
BGH 199	GMO90/epicuron200/TPGS /water 38,3/21,3/15/25,5 + 5% AC	0	unclear yellow, cubic consistency	cubic
		0.5	unclear yellow, cubic consistency	cubic
		1.5		
		3	unclear yellow, cubic consistency	cubic
		9	unclear yellow, cubic consistency	cubic
BGH 200	GMO90/epicuron200/TPGS /water 35,5/19,7/15/29,8 + 5% AC	0	unclear yellow, cubic consistency	cubic
		0.5	unclear yellow, cubic consistency	cubic
		1.5		
		3	unclear yellow, cubic consistency	cubic
		9	unclear yellow, cubic consistency	cubic
BGH 201	GMO90/epicuron200/TPGS /water 36/20/20/24 + 5% AC	0	unclear yellow, cubic consistency	cubic
		0.5	unclear yellow, cubic consistency	cubic
		1.5		
		3	unclear yellow, cubic consistency	cubic
		9	unclear yellow, cubic consistency	cubic

BGH 202	GMO90/epicuron200/TPGS /water 33,4/18,6/20/28 + 5% AC	0	unclear yellow, cubic consistency	cubic
		0.5	unclear yellow, cubic consistency	cubic
		1.5		
		3	unclear yellow, cubic consistency	cubic
		9	unclear yellow, cubic consistency	cubic

*uniform crystal distribution is observed in the cubic phase

EXAMPLE 82

Investigation of the solubility of acyclovir in compositions according to the invention

The purpose with the study is to investigate whether the presence of structurants like phosphatidylcholine and Vitamin E TPGS has any influence on the solubility of acyclovir in the liquid crystalline phase.

The compositions are treated for 1 hours in an ultrasonic bath and stored at 37°C for at least 2 days before each composition is subjected to polarized light to see whether acyclovir crystals are present in the cubic phase. If crystals are observed then the solubility is judged to be less than 2 mg/g or 5 mg/g.

The solubility of acyclovir at room temperature (22°C) is 0.5-1 mg/g.

The following compositions are tested:

1. 46.4/18.6/35 (GMO/Vitamin E TPGS/water) % w/w + 0.5% w/w acyclovir
2. 46.4/18.6/35 (GMO/Epikuron 200/water) % w/w + 0.5% w/w acyclovir
3. 34.3/13.7/32/20 (GMO/Epikuron 200/water/TPGS) % w/w + 0.5% w/w acyclovir
4. 46.4/18.6/35 (GMO/Vitamin E TPGS/water) % w/w + 0.2% w/w acyclovir
5. 46.4/18.6/35 (GMO/Epikuron 200/water) % w/w + 0.2% w/w acyclovir
6. 34.3/13.7/32/20 (GMO/Epikuron 200/water/TPGS) % w/w + 0.2% w/w acyclovir

The solubility of all the compositions is found to be less than 0.2% as acyclovir crystals are observed in the microscope. The results indicate that the lecithin and the TPGS do not increase the solubility of acyclovir compared with a GMO/water cubic phase.

EXAMPLE 83

A. Investigation of whether phosphatidylcholin together with Vitamin E TPGS form a cubic liquid crystalline phase

The following compositions are studied:

1. Epikuron 200/Vitamin E TPGS/water (% w/w)

1. 10/60/30

2. 20/50/30
3. 30/40/30
4. 40/30/30
5. 50/20/30

2. Epikuron 145/Vitamin E TPGS/water (% w/w)

6. 10/60/30
7. 20/50/30
8. 30/40/30
9. 40/30/30
10. 50/20/30

The compositions are prepared as described above (Epikuron 145 is dispersed/dissolved in Vitamin E TPGS at 60°C for up to 3 days). The compositions are inspected in polarized light as described under the heading "Methods".

The results show that no cubic phase has been formed in any of the compositions investigated.

B. Investigation of the bioadhesiveness of phosphatidylcholine/Vitamin E TPGS based compositions

The compositions described above under heading "A" are subjected to a test for bioadhesion employing test system No. 3 - washing off ability from the skin described under the heading "Methods". The results are that at least some of the compositions are bioadhesive.

EXAMPLE 84

Phase transitions of GMO 84 or GMO 90 containing compositions

A. Compositions without any drug substance

A composition of GMO 84/water 85/15% w/w is tested employing the DSC method described under the heading "Methods" above. The results are given in Fig. 4. DSC experiments give information about at which temperature a phase conversion takes place. DSC measurements alone give no information of the particular phases involved (e.g. lamellar, cubic hexagonal etc.). However, if the DSC results as in the present case are compared with e.g. results from

observation of the compositions in polarized light (see above under the heading "Methods") information on the crystalline phases as well as the transition temperature is obtained.

For the composition investigated, the results from the DSC and polarized light measurement show that the lamellar phase is present at room temperature and the lamellar phase is changed to the cubic phase when the temperature increases (Fig. 4). The transition temperature is about 37°C.

Compositions containing GMO 90 and Vitamin E TPGS and/or Epikuron 200 as structurants are subjected to X-ray diffraction measurements (as described under the heading "Methods") in a temperature scan at 20-80°C. The aim of the study is to investigate the influence structurants like Vitamin E TPGS and/or phosphatidylcholin have on the phase behaviour of GMO/water based composition. Furthermore, the aim of the study is also to obtain an indication of whether the structurants participate in the cubic structure formed due to the GMO/water content in the compositions or whether the function of the structurants more are like diluents, i.e. they do not in themselves participate in the formation of the cubic structure but may merely just be incorporated in the composition and the cubic structure is more or less alone based on the GMO/water content.

The compositions are:

1. GMO/Vitamin E TPGS/water (50/20/30 % w/w)
2. GMO/Vitamin E TPGS/water (50/15/35 % w/w)
3. GMO/Epikuron 200/water/Vitamin E TPGS (39.4/15.8/29.8/15 % w/w)

In the following results from the compositions 1-3 mentioned above at 37°C are given for illustrative purposes:

d-Spacings:

	comp. 1 and 2	ratio	comp. 3	ratio
Lipid phase	65.6Å	1	75.2Å	1
	58.1Å	0.88	60.5Å	0.80
	36.3Å	0.55	36.7Å	0.48

The results show that the compositions 1-3 are cubic at 37°C and give an indication of that Vitamin E TPGS and/or Epikuron 200 participate in the cubic structure, i.e. the cubic liquid

crystalline phase formed is based on the GMO/Vitamin E TPGS/water or GMO/Epikuron 200/water/Vitamin E TPGS compositions and not on the GMO/water content alone. These indications are supported by the observation that rather high concentrations (above 10% by weight) of Vitamin E TPGS and/or lecithin (both are soluble in GMO) can be incorporated in the GMO without any or any substantial deterioration or the cubic lattice structure. This is in contrast to what is generally observed, namely that if the lattice structure should not be substantially disturbed by the presence of an auxiliary substance, the auxiliary substances in general only can be incorporated into the GMO cubic lattice structure in a relatively low concentration. If Vitamin E TPGS and/or lecithin do not participate in the cubic lattice structure then an excess of water would have been expected, i.e. a phase separation of the composition into at least two distinct liquid phases would have been observed and no such observation is made.

The compositions Nos. 1-3 above are also subjected to DSC experiments. No peaks is observed (see Figs. 5-7) indicating that the cubic phase do not transform to another liquid crystalline phase in the temperature range investigated (20-70°C). These results are in consistency with the results obtained from the X-ray measurements given above.

B. Compositions containing acyclovir

DSC experiments as described above were also performed on compositions containing GMO/water 65/35% w/w with 5% w/w acyclovir (crystalline and micronized, respectively). The samples were stored at 5°C for two days to ensure equilibration of the sample. The lipids in the sample solidified at this temperature. The DSC was run at 5-70°C. The thermograms obtained showed only a clear melting peak at about 16-17 °C for both the reference sample (GMO/water 65/35% w/w) and the samples containing 5% w/w acyclovir. The solidified sample transfers to the cubic phase (reversible process). No phase transition of the cubic phase seemed to have taken place. The results are in well agreement with the results obtained by use of X-ray diffraction measurement described in the following.

Compositions containing GMO/water 65/35% w/w and GMO/water 65/35% w/w with acyclovir (crystalline and micronized, respectively) added in concentrations 2.5, 5.0 and 10% w/w were subjected to X-ray diffraction measurements (as described under the heading "Methods") in a temperature scan at 20-70°C. The aim of the study was to examine if the cubic phase of GMO/water 65/35% w/w is changed when acyclovir is added. In the following results from the compositions mentioned above at 37°C are given for illustrative purposes:

d-Spacings:

	crystalline	micronized	ratio
Lipid phase	61.7Å	61.7Å	1
	50.5Å	50.5Å	0.81
	36.3Å	36.3Å	0.58
	29.7Å	29.7Å	0.48
Acyclovir	12.9Å	-	-
	8.44Å	-	-
	3.74Å	3.74Å	-
	3.42Å	3.42Å	-

The results show that the compositions are cubic at 37°C.

The results obtained for all the tested compositions in the temperature range 20-70°C show that all the tested compositions are cubic in the temperature interval 20-70°C. The diffraction lines from acyclovir do not interfere with the lines from the cubic phase. In conclusion, the results indicate that acyclovir both in its crystalline and micronized form is inert in the cubic phase (probably because acyclovir has a low solubility in the cubic phase). Thus, no influence of acyclovir on the phase behaviour has been observed in the concentration range investigated and the cubic phase containing acyclovir is rather stable against temperature fluctuations.

Moreover, compositions containing GMO 90 and Vitamin E TPGS and/or Epikuron 200 as structurants and 5% w/w acyclovir (crystalline) are also subjected to X-ray diffraction measurements (as described under the heading "Methods") in a temperature scan at 20-80°C. The aim of the study is to investigate the influence of acyclovir on the phase behaviour of compositions wherein phosphatidylcholine and/or Vitamin E TPGS are added as structurants. Acyclovir is added to the compositions denoted No. 2 and 3 above under the heading "A. Compositions without any drug substance", i.e. 5% w/w acyclovir is added to GMO/Vitamin E TPGS/water (50/15/35 % w/w), composition No. 2A, and to GMO/Epikuron 200/water/Vitamin E TPGS (46.4/18.6/35 % w/w), composition No. 3A.

In the following results from the compositions 2A and 3A mentioned above at 37°C are given:

d-Spacings:

	comp. 2A	ratio	comp. 3A	ratio
Lipid phase	67.0Å	1	85.6Å	1

58.1Å	0.86	64.2Å	0.75
35.0Å	0.53	37.6Å	0.43

The results show that the compositions 2A and 3A are cubic at 37°C. Thus, acyclovir in a concentration of 5% w/w does not seem to result in a change in the phase behaviour and the cubic phase seems to be rather stable within the temperature ranges investigated. These results are supported by results from DSC experiments where no peaks is observed (see Figs. 8-9) indicating that the cubic phase do not transform to another liquid crystalline phase in the temperature range investigated (20-70°C).

Furthermore, compositions containing GMO/water 65/35% w/w with acyclovir (crystalline and micronized, respectively) added in a concentration of 1-40% were tested in polarized light at 22°C and 37°C, respectively, as described above under the heading "Methods". The results show the presence of cubic phases in all compositions indicating that acyclovir probably is inert in the cubic phase.

EXAMPLE 85

Investigation of the bioadhesiveness of compositions according to the invention

The following compositions (with or without 5% crystalline acyclovir) are tested in the washing off ability test system for bioadhesiveness described under the heading "Methods".

1. GMO/Vitamin E TPGS/water (50/20/30 % w/w)
2. GMO/Vitamin E TPGS/water (50/15/35 % w/w)
3. GMO/Epikuron 200/water/Vitamin E TPGS (39.4/15.8/29.8/15 % w/w)
4. GMO/Epikuron 200/water (55/15/30 % w/w)
5. GMO/Lipoid S75/water/Vitamin E TPGS (39.4/15.8/29.8/15 % w/w)*
6. GMO/Lipoid S75/water/Vitamin E TPGS (33.4/18.6/28/20 % w/w)*
7. GMO/Lipoid S75/water/Vitamin E TPGS (40/10/30/15 % w/w)*

* was added 0.1% w/w α-tocopherol as an antioxidant

All 14 compositions are bioadhesive and scores of about 4-5 are obtained.

EXAMPLE 86

Investigation of the dissolution/release of acyclovir from various compositions according to the invention

The dissolution rate of acyclovir in various GMO compositions is determined using Franz diffusion cells as described under the heading "Methods".

A series of GMO compositions containing Epikuron 200 (phosphatidylcholin) and/or Vitamin E TPGS and acyclovir are prepared as described above, and they are subjected to the above dissolution/release rate determination. All compositions were suspensions of acyclovir, that is, they contain acyclovir which has not dissolved. The solubility of acyclovir in the compositions investigated is less than 0.2% w/w according to the solubility experiments performed.

The following compositions are investigated:

Composition No.	composition
1	67/33 (GMO/water) % w/w + 5% w/w acyclovir
2	46.4/18.6/35 (GMO/Vitamin E TPGS/water) + 5% w/w acyclovir
3	46.4/18.6/35 (GMO/Epikuron 200/water) % w/w + 5% w/w acyclovir
4	34.3/13.7/32/20 (GMO/Epikuron 200/water/TPGS) % w/w + 5% w/w acyclovir
5	70/10/10/10 (GMO/Epikuron 200/TPGS/water) % w/w + 5% w/w acyclovir
6	GMO/oleic acid/water/acyclovir (33/5/27/5) % w/w

The release profiles for composition Nos. 1-4 are shown in Figs. 10 and 11 and the following slopes (Higuchi plots) are found:

Composition No.	slope (α)
1	1107
2	1616
3	1407
4	1254

The results show that the release of acyclovir from composition No. 4 containing Epikuron 200 as well as Vitamin E TPGS and only about 34% by weight of GMO is almost of the same order of magnitude as the release from composition No. 1 without any content of structurant and with a concentration of GMO of about 65% by weight.

With respect to compositions Nos. 5-6, the liquid crystalline phase present in composition No. 5 is the lamellar liquid crystalline phase. The composition is in the form of a precursor composition and a phase conversion to the cubic liquid crystalline phase takes place during the testing. The release rate of acyclovir (cf. Fig. 11A) is of the same order of magnitude as the reference cubic liquid crystalline phase-containing composition (GMO/water) and thus, confirms that the cubic liquid crystalline phase is formed during the test. Furthermore, at the end of the experiment a tested sample was investigated by polarised light and a cubic liquid crystalline phase was observed.

Composition No. 6 contains oleic acid as an enhancer. The liquid crystalline phase present in the composition is the reverse hexagonal crystalline phase. The release rate of acyclovir (see Fig. 11A) is of the same order of magnitude as the reference cubic liquid crystalline phase-containing composition (GMO/water) and thus, indicates that the cubic liquid crystalline phase is formed early during the test. It is most likely that oleic acid is rapidly released and then the conditions present in the composition favours a formation of the cubic liquid crystalline phase. Furthermore, at the end of the experiment a tested sample was investigated by polarised light and a cubic liquid crystalline phase was observed. Also, after 1 hour of testing a sample was withdrawn and the cubic liquid crystalline phase was observed.

In conclusion, it has been shown that i) the rate limiting step in the dissolution process is diffusion of acyclovir molecules, ii) a precursor composition is capable of generating a cubic liquid crystalline phase, and iii) a phase conversion may take place after application of a composition.

EXAMPLE 87

Compositions containing antiviral substances

In the following table is listed a number of interesting compositions. The compositions are prepared as described above. 5% w/w of an antiviral substance is added to all the compositions listed in the table below.

Vehicle	Composition % w/w
GMO/TPGS/water	45/50/35 + 5% acyclovir
GMO/TPGS/water	45/50/35 + 5% peniciclovir
GMO/TPGS/water	45/50/35 + 5% famiciclovir
GMO/TPGS/water	45/50/35 + 5% ganciclovir
GMO/TPGS/water	45/50/35 + 5% valaciclovir
GMO/TPGS/water	45/50/35 + 5% cidofovir
GMO/TPGS/water	45/50/35 + 5% lobucavir
GMO/TPGS/water	45/50/35 + 5% sorivudine
GMO/TPGS/water	45/50/35 + 5% didanosine
GMO/Epikuron 200/water	50/20/30 + 5% acyclovir
GMO/Epikuron 200/water	50/20/30 + 5% peniciclovir
GMO/Epikuron 200/water	50/20/30 + 5% famiciclovir
GMO/Epikuron 200/water	50/20/30 + 5% ganciclovir
GMO/Epikuron 200/water	50/20/30 + 5% valaciclovir
GMO/Epikuron 200/water	50/20/30 + 5% cidofovir
GMO/Epikuron 200/water	50/20/30 + 5% lobucavir
GMO/Epikuron 200/water	50/20/30 + 5% sorivudine
GMO/Epikuron 200/water	50/20/30 + 5% didanosine
GMO/Epikuron 200/water/TPGS	39.4/15.8/29.8/15 + 5% acyclovir
GMO/Epikuron 200/water/TPGS	39.4/15.8/29.8/15 + 5% peniciclovir
GMO/Epikuron 200/water/TPGS	39.4/15.8/29.8/15 + 5% famiciclovir
GMO/Epikuron 200/water/TPGS	39.4/15.8/29.8/15 + 5% ganciclovir
GMO/Epikuron 200/water/TPGS	39.4/15.8/29.8/15 + 5% valaciclovir
GMO/Epikuron 200/water/TPGS	39.4/15.8/29.8/15 + 5% cidofovir
GMO/Epikuron 200/water/TPGS	39.4/15.8/29.8/15 + 5% lobucavir
GMO/Epikuron 200/water/TPGS	39.4/15.8/29.8/15 + 5% sorivudine
GMO/Epikuron 200/water/TPGS	39.4/15.8/29.8/15 + 5% didanosine

In the following is listed a number of suitable precursor compositions containing 5% by weight of acyclovir.

GMO/Epikuron 200/TPGS/paraffin oil + 5% w/w acyclovir:
70/10/10/10
65/15/15/5
73/10/15/2

GMO/Epikuron 200/TPGS/paraffin oil/water + 5% w/w acyclovir:
69/10/10/10/1
64/15/15/5/1
72/10/15/2/1

GMO/Epikuron 200/TPGS/sorbitan ester + 5% w/w acyclovir:
70/10/10/10
65/15/15/5
73/10/15/2

GMO/Epikuron 200/TPGS/sorbitan ester/water + 5% w/w acyclovir:
69/10/10/10/1
64/15/15/5/1
72/10/15/2/1

GMO/Epikuron 200/TPGS/lanolin/water + 5% w/w acyclovir:
69/10/10/10/1
64/15/15/5/1
72/10/15/2/1

GMO/Epikuron 200/TPGS/water + 5% w/w acyclovir:
70/10/10/10
70/12/16/2
71/12/16/1

GMO/Epikuron 200/TPGS/sesame oil/water + 5% w/w acyclovir:
76/10/10/2/2
78/10/10/1/1
68/15/15/1/1

GMO/Epikuron 200/TPGS/sunflower oil/water + 5% w/w acyclovir:
76/10/10/2/2
78/10/10/1/1
68/15/15/1/1

Comments to the precursor compositions: Oil (e.g. olive oil, ricinus oil etc.) or another substance which decreases the melting point of the lipid formulations may be added to obtain a cream or an ointment at room temperature. After application on the skin or mucosa, the compositions are

able to absorb e.g. sweat or exudate from a wound and a liquid crystalline phase like e.g. the cubic liquid crystalline phase is formed.

Alternatively, a liquid crystal phase inhibitor may be added and exert its function in the solid state (e.g. sugar alcohols like trehalose, or PVP).

Addition of water in small amounts (corresponding to a concentration of 0.1-5% by weight) may reduce the viscosity and hinder crystallization of the lipids.

Other compositions are also relevant, i.e. compositions having other active substances or having a drug concentration of about 1-20% w/w and compositions having a composition of the vehicle as given in Example 1-80 above.

EXAMPLE 88

pH-solubility profile for acyclovir

Experimental

To a 100 ml Erlenmeyer flask were added 50 ml buffer solution and 250 mg acyclovir.

The buffers with pH 3.6, 4.2 and 5.3 were prepared using monobasic sodium phosphate and dibasic sodium phosphate (pH adjustment with phosphoric acid). The buffers in the pH range 6.0 to 9.6 were prepared using monobasic potassium phosphate (pH adjustment with sodium hydroxide). The molarity of the phosphate salts was 0.05M; the pH of the medium was measured with a pH-meter.

Each mixture was stirred with a magnetic stirrer for 24 hours, and after equilibrium to room temperature, the sample was passed through a membrane filter. The solution was diluted to appropriate volume and the amount of acyclovir dissolved was determined by HPLC.

The solubility of acyclovir as a function of pH is given in the table below and in Fig. 3. From the results, it is seen that the minimum solubility of acyclovir is at a pH in a range of from about 4 to about 6.

Acyclovir/Solubility at different pH

pH (buffer)	Acyclovir, mg/ml
3.6	1.9
4.2	1.8
5.3	1.8
6.0	1.8
6.6	1.9
7.6	1.9
8.5	2.2
8.8	2.5
9.0	2.5
9.2	2.9
9.6	3.5

EXAMPLE 89

Investigation of the influence of different active substances on the liquid crystalline phase

Miconazole is an example of an active substance which is insoluble in water but has a solubility of more than 2% w/w in the liquid crystalline phase. However, the release of miconazole is very slowly from the cubic phase. The table given below shows the solubility of and the crystalline phase obtained for miconazole in a GMO/water 70/30% w/w vehicle.

Miconazole (% w/w)	Solubility	Liquid crystalline phase
1	soluble	cubic
2	soluble	cubic
3	soluble	cubic
4	soluble	cubic
5	soluble	cubic
6	crystals	lamellar

For miconazole (as well as for some other substances which are soluble in the cubic liquid crystalline phase in certain concentrations) experiments have shown that the bioadhesiveness of

compositions containing the substances varies with the concentration of the substance. In the table below results are given from testing various miconazole compositions in a GMO/ethanol 60/40% w/w vehicle or in a GML/ethanol 60/40% w/w vehicle, respectively, for bioadhesiveness employing Test system No. 1.

Concentration of miconazol (% w/w)	Bioadhesion* (residual amount %)	
	GMO-based	GML-based
0	85	95
2		
3		
4	72	86
5		41
6	72	
8	33	
10		4
15		
25		

*: In the tests runs the following test conditions were employed: initial rinsing period: 5 min, initial rinsing flow: 10 ml/min, angle: -21°, flow rate: 10 ml/min, flow period: 30 min

From the results given above for the GMO-based composition it is seen that there is a dramatic fall in bioadhesiveness when the concentration of miconazole exceeds 6% w/w, i.e. when the liquid crystalline phase changes from the cubic phase to the lamellar phase and when miconazole in the liquid crystalline phase is present as crystals, i.e. when the concentration exceeds the solubility of miconazole.

The results support the results of other experiments performed by the inventors, namely that there is a close correlation between the presence of a cubic phase and occurrence of a high degree of bioadhesiveness. The other experiments performed by the inventors involved application of GMO, GMO/ethanol mixtures, GML on Test system No. 1 for bioadhesiveness. It was found that the samples applied in contact with the mucosa and washing medium all had converted into the cubic phase and that the samples were bioadhesive. The same applies for

compositions containing indomethacin (5% w/w) in a GMO/ethanol 60/40% w/w vehicle and other bioadhesive compositions containing an active substance.

From the results given above in the table it is seen that when the concentration of miconazol exceeds a certain level, the bioadhesion is severely impaired. This indicates that when the concentration of the active substance in the cubic phase exceeds a certain level, the cubic phase structure is disturbed, or another liquid crystalline phase may perhaps have been formed (the active substance and/or any excipients may alter the phase diagram).

In the case of acyclovir, however, this reduction in bioadhesiveness with increased content of acyclovir, beyond the saturation point, does not seem to influence the cubic phase and does not seem to impair the bioadhesiveness (tested by means of Test system No. 3). Experiments showing this were performed with acyclovir ointment compositions, prepared with GMO 90, with concentrations of crystalline acyclovir of 2%, 5%, 10%, 20% and 30% by weight, respectively. These compositions were found to be highly bioadhesive, indicating that with substances having a very low solubility in the liquid crystalline phase, the liquid crystalline phase remains less disturbed by the presence of particles of the active substance and retains its bioadhesive properties.

EXAMPLE 90

Investigation of the influence of different excipients or solvents on the bioadhesiveness of GMO or GML based compositions

The influence of various excipients and solvents was investigated. The various compositions were prepared as described above and the bioadhesiveness was tested using the test system No. 1. The following results were obtained:

Composition % w/w	Bioadhesion Residual amount %
GMO[a]	90
GML[a]	65*
GMO/GML[a] 40/60***	56*
Mixtures with solvents:	
GMO/water 85/15[b]	94

GML/ethanol 60/40	95**
GMO/ethanol/propylene glycol/water:	
45/30/10/15	93
Mixtures with solubilizing agents or preservatives:	
GMO/ethanol/benzyl alcohol:	
60/30/10	87**
GMO/ethanol/benzyl alcohol/water:	
60/20/5/15	80
50/20/10/20	89
Mixtures with release modulating agents:	
GMO/ethanol/glycerol:	
50/30/20	97
GMO/ethanol/sesame oil:	
59/40/1	96
58/40/2	93
50/40/10	14
50/30/20	0**
GMO/ethanol/soybean oil:	
59/40/1	98
58/40/2	93
50/40/10	22
40/20/40	0**
GMO/ethanol/lecithin:	
55/40/5	99
45/40/15	97

[a] melted gently before application

[b] lamellar phase

* lower results than expected; probably due to the reference values used in the analysis of the mixture

** test conditions: angle: -21°; initial rinsing period: 5 min; initial rinsing flow: 10 ml/min; flow rate: 10 ml/min; flow period: 30 min.

*** the GMO/GML mixture corresponds to about equal amounts of glycerol monooleate and glycerol monolinoleate

The results given above show that addition of relevant excipients or solvents such as, e.g., agents which are known solubilizers for active substances or agents which are known as release modulating agents (i.e. agents which when added make it possible to adjust or control the release of the active substance from a composition) do not significantly influence the bioadhesiveness of the composition when the agents (excipients or solvents) are added in relatively low concentrations (less than about 10% w/w). Thus, the release of an active substance from a composition which has proved to possess bioadhesive properties can be controlled at least to a limited extent by adjusting the amount of a release modulating agent such as, e.g., glycerol, sesame oil, soybean oil, sunflower oil, lecithin, cholesterol, etc. A modulating agent may influence the pore size of the water channels in the cubic phase and/or alter the partition coeffient of the active substance between the lipid domains and the aqueous phase at least to a limited extent. Furthermore, if necessary, solubilisation of an active substance or a fatty acid ester for use in a bioadhesive composition can be effected by use of e.g. benzyl alcohol without significantly influencing the bioadhesive properties of the composition. In conclusion, the bioadhesive principles described herein have a high potential with respect to developing bioadhesive drug compositions having such a drug localization, such a drug release profile, and such a drug duration which are desirable or necessary under the given circumstances. Thus, the present inventors have found an advantageous bioadhesive drug delivery system.

EXAMPLE 91

Investigation of the presence of an active substance in a liquid crystalline phase of glycerol monooleate

The methodology described herein is a methodology which is generally useful for investigating whether mixing or dissolving of an active substance in a vehicle capable of forming a liquid crystalline phase also leads to incorporation of the active substance in the liquid crystalline phase. While miconazol and lidocain hydrochlorides have been used as model substances in the description of the experiments, the same measures as described herein can be used for substances which have a very low solubility in both water and ethanol such as, e.g., acyclovir.

Furthermore, the study was performed in order to examine the recovery of the samples applied.

A lipophilic (miconazol) and a hydrophilic active substance (lidocain hydrochloride), respectively, were applied on the rabbit jejunum test model for bioadhesiveness (test system No. 1). A vehicle of GMO 84/ethanol 60/40% w/w incorporating 2% w/w of either miconazol or lidocain hydrochloride was employed. The GMO 84/ethanol vehicle is bioadhesive in itself. After a flow

period of 10 sec (corresponding to t=0), and a flow period of 30 minutes (corresponding to the end of the experiment) the samples applied were removed from the mucosa and the cubic phase was quantitatively examined by HPLC for the content of active substance. As seen from the table below almost all miconazole was found after 10 sec and 30 minutes. These results indicate that the lipophilic miconazole is incorporated in the cubic phase formed and the result at 30 minutes indicates that the drug is very slowly released from the cubic phase. This is consistent with release experiments of miconazole delivered from a cubic phase into a 0.05 M phosphate buffer solution, pH 6.5 (37°C). Miconazole seems to prefer the lipophilic part of the cubic phase. The results are given in the following table; results for an acyclovir composition are also given.

Composition	Flow period	Recovery of active substance % mean of two determinations
GMO 84/ethanol/miconazol:		
58.8/39.2/2	10 sec	85
	30 min	93
GMO 84/ethanol/lidocain HCl:		
58.8/39.2/2	10 sec	37
	30 min	7
GMO 90/acyclovir		
95/5	10 sec	87
	30 min	65

In the experiment with lidocaine hydrochloride, barely half the content of the drug was recovered after a flow period of 10 sec and only a negligible amount after 30 minutes. Because of its high water solubility (about 0.7 g/ml at 25°C), the greater part of the lidocaine hydrochloride is probably dissolved and washed away in the buffer solution during the prehydration time (10 min) and only some is incorporated in the cubic phase formed. Most of the incorporated drug had been released at the end of the experiment. Other studies have shown that lidocaine hydrochloride is released rather quickly from the cubic phase probably through the water channels contained in the cubic phase.

Results for acyclovir, which is poorly soluble in both water and the cubic phase, given in the table clearly demonstrate that acyclovir is enclosed in the cubic liquid crystalline phase formed and some of it may have been released during the experiment.

In conclusion, the experiments reported above indicate that formulations in which GMO and an active substance are dissolved in ethanol or the active substance suspended in GMO 90, serve as a precursor for the formation of a cubic phase formed in situ, and that the active substance is incorporated in the cubic phase formed.

EXAMPLE 92

Dissolution/release rate of a bioadhesive composition containing acyclovir

The dissolution rate of acyclovir in various GMO compositions was determined using Franz diffusion cells as described under the heading "Methods".

A series of GMO compositions containing acyclovir were prepared as described above, and they were subjected to the above dissolution rate determination. All compositions were suspensions of acyclovir, that is, they contain acyclovir which was not dissolved. The solubility of acyclovir in the compositions investigated was less than 0.1% w/w (0.05% w/w<the solubility of acyclovir<0.1% w/w).

The results appear from Figures 12-18. The results indicate that the release of acyclovir from a GMO based vehicle is dependent on the concentration of acyclovir in the composition, provided that the release takes place from a cubic phase system. Furthermore, the results indicate the capability of a GMO-based vehicle to function as a very effective drug delivery system.

Figs. 12-14 show the release of acyclovir (1-5% micronized) from a cubic phase (GMO/water 65/35% w/w) and Zovir® cream, respectively, into isotonic 0.05 M phosphate buffer solution, pH 6.5 (37°C). As appears from the graph of Fig. 12 showing the cumulative release of acyclovir, the release of acyclovir increases with increasing concentration of acyclovir over the range investigated. There is not proportionality between the rate of release and the concentration; this appears from the fact that the graphs of % released (Fig. 13) do not coincide and the slope of the Higuchi plots (Fig. 14); the release is dependent on the concentration. However, at a concentration of 3-5% w/w acyclovir, no significant difference in release rates was found.

It is justified to refer to rate constant herein as the release of acyclovir from the liquid crystalline formulations according to the invention which can be described by means of the so-

called Higuchi equation (Higuchi, T., Rate of release of medicaments from ointment base containing drug in suspension. J. Pharm. Sci., 50 (1961) 874-875): on linear regression; the cumulative amount of acyclovir released plotted versus the square root of time results in a straight line with the slope k (rate constant $\mu g/h^{1/2}$). This appears from Fig. 14 which shows the plots for a number of compositions containing acyclovir in concentrations from 0.99% by weight to 4.76% by weight in comparison with Zovir® cream containing 5% by weight of acyclovir. The slopes of the graphs in Fig. 14 are as follows:

Zovir® cream, 5%:	155
Acyclovir 0.99% w/w:	410
Acyclovir 1.96% w/w:	587
Acyclovir 2.91% w/w:	717
Acyclovir 3.85% w/w:	773
Acyclovir 4.76% w/w:	1016

The higher the acyclovir concentration is, the smaller the percentage of acyclovir released. Acyclovir must first be dissolved before it is released from the cubic phase, probably through the water channels. Comparing the release profiles for 1% micronised and crystalline acyclovir, respectively, gives identical release profiles and indicates that the rate limiting step is diffusion of dissolved acyclovir rather than dissolution of the suspended acyclovir. In spite of this, and in spite of the low solubility of acyclovir both in water and in the cubic phase, the release of acyclovir from the composition according to the invention is dramatically increased compared to the Zovir® cream. Thus, a comparison of the rate constant for acyclovir (5%) released from Zovir® cream and GMO/water 65/35% w/w shows that the rate constant is about 6 times larger for the latter (Fig. 14).

With a view to testing if the rate of release can be improved by means of micronized acyclovir, as opposed to crystallinic acyclovir, the release from various compositions was examined. Figures 15, 16 and 17 show an identical release pattern for crystalline and micronized acyclovir, respectively, from a formulation consisting of GMO/water 65/35% w/w + 1% acyclovir. On the other hand it appears that the release rate of crystalline acyclovir is slightly improved from a composition containing lecithin (GMO/water/lecithin 55/35/10% w/w + 1% acyclovir) compared to the same composition containing micronized acyclovir (Figs. 15-16). However, no significant difference is found. By comparing the release profiles for compositions consisting of GMO/water 65/35% w/w containing 5% crystalline and 5% micronized acyclovir, respectively (Fig. 17), it seems that the release rate has increased somewhat with the micronized quality. On the other hand other studies have indicated that the release rate of acyclovir from a composition consisting of GMO/water/glycerol % w/w + 5% acyclovir is identical for the crystallinic and the micronized

quality. Whether the release is improved by application of a micronized quality as opposed to a crystalline quality depends on the composition of the cubic phase. However, more experiments have to be carried out to exclude that the differences observed arise from experimental variation. The results from the release experiments with micronized and crystalline acyclovir, respectively, indicate that the rate limiting step is diffusion of dissolved acyclovir and not dissolution of suspended acyclovir.

The micronized quality increases the viscosity of the cubic phase more that the crystalline phase. This condition alone favours the use of the crystalline quality in a potential product so that product of suitable and not too high viscosity can be obtained. Furthermore, the use of the crystalline form is favourable from a stability point of view.

The release of acyclovir from various GMO compositions containing 1% w/w and 5% micronized acyclovir, respectively, containing release modulating or solubilising compounds was examined and compared with the release from a cubic phase consisting of 65 parts of GMO and 35 parts of water (Figs. 16-17). All the compositions except the compositions containing sesame oil and the composition containing GMO/glycerol 65/35 % w/w were the cubic phase, as evidenced in polarised light. As can be seen from the release profiles in Fig. 18 for the compositions containing 1% acyclovir, the profile of GMO/water 65/35 % w/w (reference) has a shape similar to the others with the exception of the profiles for the compositions containing sesame oil. In the latter case the release rate is drastically reduced, which could mean that the compositions consist of the reversed hexagonal phase, but this has not been confirmed. It should be noted that the composition consisting of 65 parts of GMO and 35 parts of glycerol, have the same release profile as the reference composition, although both the visual and the polarized light do not indicate that they consist of the cubic phase. It is possible however, that the cubic phase is created on the surface of the formulation during the release experiment, through its contact with the dissolution medium (37°C). Addition of the release modulating substances glycerol and lecithin (lecithin is as described above also a structurant) to the cubic phase has not significantly changed the release of acyclovir in the concentrations examined. Neither does the TPGS seem to have increased the dissolution of acyclovir in the cubic phase nor changed the partition coefficient between the cubic phase and the release medium, as the release profile is identical with the profile of the reference composition. Fig. 11 shows the release profiles of composition containing 5% acyclovir. The release profiles for the compositions containing glycerol and lecithin are identical while the release profile of the reference composition is somewhat smaller. This indicates that the release of acyclovir is slightly increased from the compositions added release modulation agents, however, the improvement is modest and the difference observed is not significant. The tests indicate that it is difficult to change the release of acyclovir significantly. There are limited possibilities for changing the release if the cubic structure is to be preserved.

EXAMPLE 93

Investigation of the influence of various pharmaceutically acceptable excipients i) on the formation of a cubic liquid crystalline phase and ii) on the bioadhesiveness of GMO-containing compositions

In the table below is given the various compositions tested and the results of the tests employed.

Composition	Phase condition (polarized light, 22°C)	Bioadhesion (washing-off ability)
GMO/lactose/water 50/20/30 % w/w	cubic, undiss.	+ (score 4)
GMO/HPC/water (hydroxypropyl-cellulose is dissolved in water) 50/20/30 % w/w		+
GMO/HPC/water (hydroxypropyl-cellulose is dissolved in GMO) 50/20/30 % w/w		+
GMO/sorbitan ester/water 50/20/30 % w/w	cubic	+
GMO/polyethylene glycol 200/water 50/20/30 % w/w	non-cubic	+ (score 4)
GMO/propylene glycol/water 50/20/30 % w/w	non-cubic	not bioadhesive
GMO/paraffin oil/water 50/20/30 % w/w	non-cubic	not bioadhesive
GMO/lanolin/water 50/20/30 % w/w		not bioadhesive

EXAMPLE 94

Phase diagram for GMO/Vitamin E TPGS/water systems

Initial investigation of the phase diagram for GMO/Vitamin E TPGS/water systems at room temperature shows the following:

Composition of GMO/Vitamin E TPGS/water (% w/w)	Phase
60/10/30	cubic
45/20/35	cubic
46.4/18.6/35	cubic
50/15/35	cubic
55/15/30	cubic
50/20/30	cubic
41.8/23.2/35	
45/25/30	
40/30/30	non-cubic
30/40/30	non-cubic
20/50/30	non-cubic

The results are shown in Fig. 19.

EXAMPLE 95

Case stories on treatment of cold sores - preclinical study in humans

A composition of GMO/water 65/35% w/w with 5% w/w acyclovir has been used for the treatment of cold sores in humans.

Treatment was started with a maximum of 24 hours delay from start of symptoms. In one case, treatment with Zovirax® cream was tried for 4.5 days before switch to GMO acyclovir cream. GMO acyclovir cream was applied 3 times daily (range 2-4) for 2.5 days (range 1.5-4).

The results of the study are given in the Table below.

Case	Demographics	Daily applications	Treatment duration (days)	Outcome	Side effects
1	38 year ♀	3	2	Symptoms ceased. Superficial ulceration for one week	Erythema
2	50 year ♂	3	2,5	Symptoms ceased	None
3	52 year ♀	2	2,5	Symptoms ceased	None
4	29 year ♀	4	4	Symptoms improved	None
5a	38 year ♀	2	4	Ulceration	Treatment stopped due to dry skin
5b	38 year ♀	2	3	Symptoms ceased	Treatment stopped. Ulceration healed in 2 weeks. Erythema 2 weeks
6	35 year ♂	3	1,5	Healing	None
7	30-40 year ♂	No information	2-3	7/8 improved 1/8 no effect	None
Summary		Median 3 (2-4)	Median 2,5 (1,5-4)		5/7 None 2/7 erythema 1/7 ulceration 1/7 dry skin

In 7 of 8 treatments symptoms ceased or improved very much. In one case, ulceration occurred and treatment was stopped. Healing was only reported in one case, probably because the treatment prevented the typical ulceration of a cold sore.

Side effects were noted by 2 to 7 persons. One of these persons received two treatments and in both cases, treatment was stopped due to side effects. The side effects reported were ulceration, transient erythema and dry skin. No severe or serious side effects were reported.

The reported case stories do not represent scientific evidence of the efficacy of GMO acyclovir cream. They do, however, indicate that the characteristics of GMO/water 65/35% w/w with 5% acyclovir on certain points differ from those of Zovirax® cream from Glaxo Wellcome. GMO/water 65/35% w/w with 5% acyclovir adheres firmly to skin. Therefore fewer daily applications of GMO/water 65/35% w/w with 5% acyclovir were administered than what is recommended for Zovirax® cream. In 6 out of 8 cases, treatment could successfully be stopped after 2-3 days. This is shorter than the normally recommended treatment period for Zovirax® cream of 5 to 10 days.

Application frequency and treatment duration for GMO acyclovir cream in these case reports are less than recommended for Zovirax® cream. By the persons treated, the efficacy was judged to be equivalent or better than that of Zovirax® cream.

EXAMPLE 96

A. Skin irritation of GMO-containing compositions

Purpose

Evaluation of skin irritation level for four GMO-based test formulations by a cumulative evaluation performed on intact human skin compared with four commercially available products.

Natusan ointment (negative control)

Klorhexidin cream 1% (positive control)

Zovir® cream (acyclovir cream, control)

GMO in paraffin 20% (w/w) (test) Batch no. BGH 271

GMO/Epicuron 200/water 50/20/30 (w/w) (test) Batch no. BGH 269

GMO/Epicuron 00/water/TPGS 35.5/19.7/29.8/15 (w/w) (test) Batch no. BGH 270

The test was performed on nine healthy volunteers.

The test was performed over five working days with four applications and four recordings after 24 hours. The test material was applied onto the volunteers on volar next to their non-dominant underarms.

Approx. 30-35 mg of each test material was placed under the skin under a 8 mm ø aluminum chamber (Finn Chamber, Epitest Ltd OY) positioned on a sticking plaster of non-occlusive type (Scanpor, Norges Plaster). The volunteer removed the plaster the morning after application. The result was recorded approximately two hours later in connection with a fresh application of the test material. On day 5 only one recordal was made. In connection with the recordal, a photo was also taken.

The skin reaction was evaluated both in respect of erythema and oedema on a scale ranging from 0 to 3. The scoring was made by the same person for all the volunteers.

Each product was applied four times in the same place and was left for 21-23 hours. If a product caused a third degree irritation, the product in question was taken out of the testing of the volunteer in question.

Evaluated on total score, Zovir® cream, GMO/Epicurean/TPGS and GMO/Epicuron were at the same low level. GMO 20% and Natusan caused no irritation.

In this test, GMO formulations containing Epikuron 200 have caused reactions at the same level as the commercially available Zovir® cream. Consequently, they are considered suitable for pharmaceutical formulations.

B. Skin irritation of compositions with 5% acyclovir

The following compositions are tested:

1.	Paraffin oil (negative control)	
2.	0.5 Sodium lauryl sulfate (positive control)	
3.	Klorhexidin® cream 1% (positive control and reference)	
4.	Zovirax® cream 5%	
5.	Vectavir cream 1%	
6.	GMO/Epikuron 200/water	50/20/30 + 5% acyclovir (% w/w)
7.	GMO/Vitamin E TPGS/water	50/20/30 + 5% acyclovir (% w/w)
8.	GMO/Epikuron 200/TPGS/water	*33.4/18.6/20/28 + 5% acyclovir (% w/w)
9.	GMO/Epikuron 200/TPGS/water	*41.3/16.5/15/27.2 + 5% acyclovir (% w/w)
10.	GMO-90/water	65/35 % w/w
11.	GMO/Epikuron 200/TPGS	45/10/15/30 + 5% acyclovir (% w/w)

*: Stability testing at 25°C and 60% relative humidity has shown that the composition is in the form of a cubic liquid crystalline phase which is stable for at least 9 months.

The Chamber Scarification Test is used in order to evaluate the skin irritation profile of the above-mentioned compositions.

The Chamber Scarification Test is developed to investigate and compare cosmetics, cosmetic ingredients and consumer products intended for repeated use on normal or diseased skin. The assay amplifies irritant reactions to the test products by scarification of the test area prior to the first application. The test is carried out as described by K. E. Andersen in Contact Dermatitis 1996 (34), pp. 181-184 by P. J. Frosch & A. M. Kligman in Contact Dermatitis 1976 (2), pp. 314-324.

EXAMPLE 97

In vitro permeability of compositions according to the invention across human skin

Test compositions

1.	GMO/Vitamin E TPGS/water	45/20/35% w/w + 5% w/w acyclovir
2.	GMO/Epikuron 200/water	50/20/30% w/w + 5% w/w acyclovir
3.	GMO/Epikuron 200/water/TPGS	39.4/15.8/29.8/15% w/w + 5% w/w acyclovir
4.	Zovir® 5%, Wellcome (containing 5% w/w acyclovir)	BFJ15-6
5.	GMO/water	65/35% w/w + 5% w/w acyclovir

Preparation of skin membranes

Excised abdominal skin from humans was obtained from The Clinic of Plastic Surgery. The hairs were removed from the epidermal side by clipping. Subcutaneous fat on the dermal side was removed. The skin was washed with distilled water and stored at -18°C until use.

Apparatus

Franz diffusion cells having an available diffusion area of 1.77 cm^2 were used. The epidermal side of the skin was exposed to ambient laboratory conditions while the dermal side was bathed with the receptor medium consisting of 6.8 ml of 0.05 M phosphate buffer, pH 6.5. Each cell was placed on a magnetic stirrer. The temperature of the water flowing in the closed circulatory system was kept at 37°C.

Permeation procedure

The skin membranes were thawed and mounted in Franz diffusion cells. The receptor chambers were filled with receptor medium and the epidermal side of the skin was wetted with a few drops of receptor medium. The skin was then allowed to equilibrate for about 24 hours. Blood and soluble enzymes were at the same time washed out of the skin, and thereby could not disturb analysis of the receptor medium for acyclovir. The integrity of the individual skin samples was ensured by measuring the capacitance of the skin. Skin samples with a capacitance of less than about 0.055 μF were considered intact, whereas skin samples with a higher capacitance were considered damaged. The water permeability (^3H) may also be determined as a measure of the integrity of the skin. Before application of the test substances, the receptor medium was replaced by fresh media. 300-350 mg of the test substance was spread across the

entire epidermal surface in an even layer. At appropriate intervals (t=0, 6 hours, 1, 2, 3, 4 and 5 days) 2 ml samples were withdrawn and replaced by fresh receptor medium keeping an infinite sink. Due to variation when using biological membranes, at least six permeation studies were performed on each test substance.

The results from the permeation study (see Fig. 21) shows that the permeation profiles for acyclovir from the GMO/water composition (cubic liquid crystalline phase) and Zovir®, respectively, are not significantly different. The lag time is about 1 day. The release profile shows tht acyclovir delivered from a cubic liquid crystalline phase of GMO permeates the skin and, accordingly, a cubic liquid crystalline phase is an excellent drug delivery system for acyclovir and most likely also for other active substances especially antiviral substances. During the experiment which lasts for 4-5 days, the compositions remain on the skin.

However, release tests <u>in vitro</u> have shown that acyclovir incorporated into a cubic phase of GMO (GMO/water 65/35% w/w + 5% acyclovir) is released approx. 5-6 times faster than acyclovir from Zovir® cream.

Permeation experiments across epidermis (pig) isolated by heat separation gave the same results.

EXAMPLE 98

In vitro permeability of compositions according to the invention across human skin

A. Wholly skin

In order to evaluate the influence of the compositions on the ability of acyclovir or other antiviral compounds to penetrate the stratum corneum and to accumulate in the epidermis and the dermis, the following experiments can be performed using wholly intact human skin excised from cosmetic surgery. The skin is obtained from clinics for plastic surgery. The skin is treated as mentioned in the Example above and stored at -18°C. Skin from other mammals than humans may also be employed such as, e.g. guinea pigs, mice and pigs. The skin may be separated into epidermis and dermis by exposing the skin to hot water (60°C) for e.g. 45 seconds (heat separation) or by slicing with a dermatome (mechanical separation) for permeation or penetration studies. The stratum corneum can be isolated by tape stripping. If the drug substance is insoluble in water, the epidermis can be separated by dry heat separation e.g. at 60°C for 2 min by placing the sample (contained in a closed package) in a water bath or in a heat cabinet. The test conditions are generally as described in the Example above, but other test

times (e.g. from 1 hour to 7 days), amounts of sample applied (e.g. 50-350 mg) etc. may be appropriate. To avoid intra-individual variations the same donor is used to testing different compositions and the skin specimens were taken from the same skin area. In order to simulate injured skin, the skin can be injured by applying a skin enhance or by stripping the skin with tape.

The amount of drug substance within the skin can be calculated by measuring the concentration of the drug substance in i) the receptor medium, ii) the skin, and/or iii) the remaining composition. By measuring i) and iii), the amount of drug substance in the skin can be calculated.

B. Different layers of the skin

The herpes virus replicate in the living epidermis. The basal layer of the epidermis appears to be the primarily site of antiviral activity in cutaneous HSV-1 infections, i.e. the epidermis appears to be the target site for antiviral drug substances.

Permeation (i.e. penetration into and through the skin) of acyclovir or other antiviral substances can be investigated across isolated epidermis by diffusion (as described above). In this manner, a measure is obtained of the amount of acyclovir having permeated the epidermis. Alternatively, a picture is obtained of the penetration (i.e. the entry into the skin but not through the skin) of acyclovir (or other antiviral substances) in the skin by means of diffusion test using wholly skin which at the end of the experiment is divided into stratum corneum (e.g. enzymatic degradation or tape stripping; tape stripping: 10-20 x, e.g. using Scotch Brand Magic Tape No. 810 from 3M, Minneapolis, U.S.A.), epidermis and dermis by means of a dermatome. The individual layers are analyzed for acyclovir (or other antiviral substances), e.g. by liquid scintillation.

Before the tape stripping the compositions are removed by use of a spatula and the skin is dried using Kleenex dipped in a ethanol-water (3:1) solution.

In those cases where radioactive acyclovir (or other radioactive antiviral drugs) are used, the amount of acyclovir penetrating the tissue was measured by a liquid scintillation technique (^{3}H-acyclovir is commercially available in form of a ethanol/water 30/70 solution (Sigma); e.g. 21 µl ^{3}H-acyclovir corresponding to about 0.8 µCi/ml is added to 1 g composition).
Due to the fact that the main part of the acyclovir is present in the form of undissolved particles in a concentration of about 1-10% by weight, it is initially necessary to dissolve cold acyclovir and add the hot radioactive form on dissolved form in order to obtain a homogeneous mixture of cold and hot molecules. Cold acyclovir is dissolved in 0.1 N NaOH and the hot acyclovir is added

under stirring. Hydrochloric acid (to adjust pH to about 7) is rapidly added under vigorous stirring to obtain a uniform precipitation of hot and cold acyclovir crystals. The precipitation is enhanced by maintaining the mixture at 5°C for e.g. 24 hours. Then the acyclovir crystals are filtered off and washed 3 times with a small amount of water. The crystals are dried in an excicator. By using this procedure it is possible to control the ratio between hot and cold acyclovir in dissolved and undissolved form, respectively.

In order to examine the content of acyclovir in different skin sections/layers, the skin sections were placed in scintillation vials with e.g. Soluene 350 over night to dissolve the skin components. Scintillation cocktail (e.g. Hionic-Flour) was subsequently added and the samples were assayed for content of acyclovir (or the appropriate antiviral drug) by liquid scintillation spectrometry. The drug metabolizing enzyme activity in the epidermis is greatly dependent on tissue viability. Therefore, it should be stressed that the determination of skin absorption described above does not distinguish between the intact antiviral drug and its metabolites. It cannot be excluded that excised skin (usually stored) will loose some of its original enzyme activity. However, acyclovir exhibits no known metabolism in the skin.

By extracting acyclovir from the skin components, acyclovir can also be quantified by HPLC.

EXAMPLE 99

Permeation of compositions containing acyclovir or other drugs by means of an in vitro cell culture model

The permeation of acyclovir or other antiviral drugs delivered from various compositions according to the invention can be examined using in vitro cell cultures as a model of e.g. human oral epithelium. A model involving e.g. TR 146 cell (from the Royal Danish School of Pharmacy, Copenhagen, Denmark) is suitable for sensitivity and permeability studies of antiviral drugs. Other cell culture models are also available, e.g. for the testing of the efficacy of drugs.

EXAMPLE 100

Permeation of compositions containing acyclovir or other antiviral drugs by means of an in vivo animal model

The herpes virus replicate in the living epidermis. The basal layer of the epidermis appears to be the primary site of antiviral activity in cutaneous HSV-1 infections, i.e. the target for antiviral drugs. Methods - using hairless mouse or guinea pig as an animal model - are available. The

methods allow calculation of the target site concentration of the antiviral (e.g. acyclovir) drug applied and allow an estimation of the efficacy of the antiviral compositions tested (see. e.g. Lee, P.H. et al., Pharm. Res. 9, 8, pp 979-988, 1992 and Su, M.-H. et al., Drug Develop. Ind. Pharm. 20 (4), 685-718, 1994). In the following is described model systems suitable for testing the antiviral effect of the compositions according to the invention.

Animal models often used are the hairless mouse model (5-7 weeks old) and the guinea pig model. The guinea pigs are shaved on their back before the start of the experiment in order to make a hairless test area.

The animals are anaesthetized before inducing skin lesions, e.g. on the lateral side of the body or in the lumbosacral area. 0.005-0.2 ml of a virus suspension [herpes simplex virus type 1 (HSV1), e.g. strain E-377 or E-115 (titer usually in a range of 10^6 - 10^8 plaque forming units (PFU)/ml), stored at -70°C until use] was injected or rubbed on the skin with a cotton swab saturated with the virus (a drop of the virus suspension is applied on the test area and then 6 small holes are made by means of a scalpel. The test area on the skin of the test animal can be divided into several test areas, e.g. six areas, thereby allowing e.g. two different compositions (2x2) and their controls (1x2), placebo) to be tested at the same time on the same animal. Usually 10-30 animals are used for each composition (the number of animals depends on the number of applications). The infection induced by the virus generated skin lesions which appeared at the area of inoculation. Shortly after virus inoculation (e.g. 24-48 hours) compositions with antiviral drugs were applied on the test areas at the skin e.g. with a 1 ml syringe and samples are blindly randomized. The lesions are treated with the compositions for 2-10 days (applied 2-5 times daily) and then the effect of the treatment was investigated. The lesions were scored for each animal and two distinct antiviral assessments can be made: i) topical efficacy is determined by measuring the antiviral activity of the antiviral drug substance (e.g. acyclovir) delivered from the compositions tested, and ii) systemic efficacy is determined by measuring the antiviral activity of the antiviral drug substance (e.g. acyclovir) in the circulatory system which delivers the antiviral substance to the target site (presumably the epidermal basal layer).

In order to quantify the effect of the different compositions, a score system is used. Different score systems may be employed based on the appearance of the skin lesions at various times after inoculation. The score system could be that of Alenius and Öberg, Archives of Virology 1978, 58, 277-288, where the course of infection is divided into a phase of progression denoted by scores with Arabic numerals and into a phase of regression denoted by scores with Roman numerals. E.g. the inoculated areas can be scored for symptoms daily, starting 24 hours after inoculation and ending after 4-20 days, giving scores during the development of vesicles and their subsequent drying and crusting. The length and size of skin lesions can also be measured.

A low cumulative score of a composition indicates a good efficacy compared to a placebo composition (control) which generally gives a high score.

During the test HSV-1 virus may be isolated from the lesions and the number is counted. The results give an indication of i) inactivation of virus, ii) effect of the antiviral composition applied etc.

EXAMPLE 101

Clinical development programme of GMO acyclovir cream for herpes labialis

The following parameters are suggested for all clinical studies:

Setting

Outpatients from GPs, dermatologists or hospital clinics. Primary recruitment possible in connection with a Herpes simplex eruption that are not included in the study. Patients receive study medication and are instructed to start treatment immediately upon recurrence of prodromes and to return to investigator after start of treatment.

Inclusion criteria

Clinically confirmed history of recurrent Herpes Labialis, 2-3 annual recurrences. Present prodromal symptoms of Herpes Labialis eruption.

Exclusion criteria

Herpes labialis with ulceration or crusts
Immunodeficiency
Allergy to acyclovir/GMO

Efficacy parameters

Duration days/hours from start of treatment to cessation of symptoms caused by virus replication, including pain, weal, numbness and erythema.
Duration days/hours form start of treatment to crust formation.
Duration days from start of treatment to complete skin healing.

Safety parameters

Local reactions to cream administration, including a 28-30 day follow-up.

Dose finding

The experience from individual case reports indicates that fewer daily applications of GMO acyclovir compared to Zovirax® are required to obtain efficacy. The optimal administration frequency will have to be determined.

Study groups:
Placebo
Once daily
Twice daily
Three times daily

If more than three daily applications is required, GMO acyclovir is not considered to have any advantage compared to Zovirax® cream.

At present no data are available on the statistical variation of efficacy parameters, therefore a proper dimensioning of the study has not been possible. It is assumed that between 100 and 200 patients per study group is required.

Pivotal studies

It is assumed that two identical or at least very similar studies must be performed.

Study groups
Placebo
GMO acyclovir x times daily
Zovirax® 5 times daily

The argument for including a placebo group in the pivotal study is to document that the expected clinical equivalence between Zovirax® and GMO acyclovir is not a consequence of both products inefficiency.

At present no data are available on the statistical variation of efficacy parameters, therefore a proper dimensioning of the studies has not been possible. It is assumed that between 100 and 200 patients per study group is required.

CLAIMS

1. A pharmaceutical composition for administration of an active substance to or through a nail or a damaged or undamaged skin or mucosal surface of a mammal, the composition comprising

i) a first substance which is the active substance,

ii) an effective amount of a second substance which, together with a liquid medium, is capable of generating a liquid crystalline phase in which the constituents of the composition are enclosed, the liquid crystalline phase being selected from the group consisting of: a cubic, a hexagonal, a reverse hexagonal, a lamellar, and a reverse micellar liquid crystalline phase,

iii) a structurant which together with said second substance and a liquid medium is capable of forming a liquid crystalline phase selected from the group consisting of: a cubic, a hexagonal, a reverse hexagonal, a lamellar, and a reverse micellar liquid crystalline phase; and

iv) optionally, a liquid medium which is substantially homogeneously distributed in the composition,

the composition either being one in which the liquid crystalline phase has been generated by the second substance and the structurant together with a sufficient amount of a liquid medium originally present in the composition, or the composition being in a precursor form in which the second substance and the structurant have not generated the liquid crystalline phase, but are capable of forming the liquid crystalline phase <u>in situ</u> with moisture from the surface on which the composition is applied, the moisture in this case constituting at least part of the liquid medium,

the pH of the liquid crystalline phase being in the range of 3.0-9.0, determined as described herein,

the active substance having

i) a first solubility in the liquid crystalline phase of at the most 20 mg/g at 20°C, and

ii) a second solubility in water of at the most 10 mg/ml at 20°C, the water, where applicable, being buffered to a pH in a range of 3.0-9.0,

with the proviso, where applicable, that the composition is not one consisting of either a) 5% by weight of acyclovir and 95% by weight of a glycerylmonooleate/water/lecithin (55/35/10 w/w) formulation, wherein the glycerylmonooleate product is DIMODAN® GMO-90 and the lecithin is Epikuron 200, or b) 5% by weight of acyclovir and 95% by weight of a glycerylmonooleate/water/d-α-tocopherylpolyethyleneglycol 1000 succinate (65/35% w/w glycerylmonooleate/water plus 5% w/w d-α-tocopherylpolyethyleneglycol 1000 succinate), wherein the glycerylmonooleate product is DIMODAN® GMO-90.

2. A pharmaceutical composition for administration of an active substance to a mammal, the composition comprising

i) a first substance, which is the active substance,

ii) a second substance which together with a liquid medium is capable of forming a liquid crystalline phase at room temperature, the liquid crystalline phase being selected from the group consisting of: a cubic, a hexagonal, a reverse hexagonal, a lamellar, and a reverse micellar liquid crystalline phase,

iii) a structurant

which - together with said second substance and water - at room temperature is capable of forming a liquid crystalline phase selected from the group consisting of: a cubic, a hexagonal, a reverse hexagonal, a lamellar, and a reverse micellar liquid crystalline phase,

which in itself together with water can form a liquid crystalline phase selected from the group consisting of: a cubic, a hexagonal, a reverse hexagonal, a lamellar and a reverse micellar liquid crystalline phase,

which - in a two component system wherein the structurant is one of the components and water is the other - is not capable of forming a cubic liquid crystalline phase at room temperature, and

which has a solubility in said second substance of at least 15% by weight at 60°C; and

iv) optionally, a liquid medium which is substantially homogeneously distributed in the composition,

the composition either being one in which the liquid crystalline phase has been generated by the second substance in combination with the structurant and together with a sufficient amount of the liquid medium originally present in the composition, or the composition being in a precursor form in which the second substance and the structurant have not generated the liquid crystalline phase, but are capable of forming the liquid crystalline phase in situ with moisture from the site at or to which the composition is administered, the moisture in this case constituting at least part of the liquid medium, and

the composition being substantially homogeneous and having such a physical stability that substantial no irreversible phase separation into two or more distinct phases can be observed visually after storage of the composition at 25°C and 60% relative humidity for one week, and

with the proviso, where applicable, that the composition is not one consisting of either a) 5% by weight of acyclovir and 95% by weight of a glycerylmonooleate/water/lecithin (55/35/10 w/w) formulation, wherein the glycerylmonooleate product is DIMODAN® GMO-90 and the lecithin is Epikuron 200, or b) 5% by weight of acyclovir and 95% by weight of a glycerylmonooleate/water/d-α-tocopherylpolyethyleneglycol 1000 succinate (65/35% w/w glycerylmonooleate/water plus 5% w/w d-α-tocopherylpolyethyleneglycol 1000 succinate), wherein the glycerylmonooleate product is DIMODAN® GMO-90.

3. A pharmaceutical composition for administration of an active substance to a mammal, the composition comprising

i) a first substance which is the active substance,

ii) a second substance which together with a liquid medium - at room temperature is capable of forming a liquid crystalline phase selected from the group consisting of: a cubic, a hexagonal, a reverse hexagonal, a lamellar, and a reverse micellar liquid crystalline phase,

iii) a pharmaceutically acceptable excipient in a concentration of at least 5% by weight based on the total composition, and

iv) optionally, a liquid medium which is substantially homogeneously distributed in the composition,

the composition either being one in which the liquid crystalline phase has been generated by the second substance together with a sufficient amount of the liquid medium originally present in the composition, or the composition being in a precursor form in which the second substance

has not generated the liquid crystalline phase, but is capable of forming the liquid crystalline phase in situ with moisture from the site at or to which the composition is administered, the moisture in this case constituting at least part of the liquid medium,

the composition being substantially homogeneous and having such a physical stability that substantial no irreversible phase separation into two or more distinct phases can be observed visually after storage of the composition at 25°C and 60% relative humidity for one week,

the composition containing at the most about 60% by weight of said second substance, and

with the proviso, where applicable, that the composition is not one consisting of either a) 5% by weight of acyclovir and 95% by weight of a glycerylmonooleate/water/lecithin (55/35/10 w/w) formulation, wherein the glycerylmonooleate product is DIMODAN® GMO-90 and the lecithin is Epikuron 200.

4. A composition according to claim 3, wherein the pharmaceutically acceptable excipient has a solubility of less than about 15% such as less than about 12.5%, 10%, 7.5%, 5%, 2% or 1% by weight in said second substance at 60°C.

5. A composition according to claim 3, wherein the pharmaceutically acceptable excipient has a solubility of more than about than about 15% such as more than about 25%, 30% or 50% by weight in said second substance at 60°C.

6. A composition according to any of claims 2-5, wherein the active substance has

i) a first solubility in the liquid crystalline phase of at the most 20 mg/g at 20°C, and

ii) a second solubility in water of at the most 10 mg/ml at 20°C, the water, where applicable, being buffered to a pH in a range of 3.0-9.0,

7. A composition according to claim 1 or 6, wherein the second solubility of the active substance is determined at a pH which is substantially identical to the pH prevailing in the liquid crystalline phase, determined as described herein.

8. A composition according to claim 1 or 6, wherein the second solubility of the active substance is the minimum aqueous solubility at a pH in the range of 3.0-9.0, determined as described herein.

9. A composition according to any of claims 2-5, wherein the active substance has a solubility in water of at least about 10 mg/ml at 20°C, the water, where applicable, being buffered to a pH substantially identical to the pH prevailing in the liquid crystalline phase, determined as described herein.

10. A composition according to claim 2 or 3, wherein the solubility of the active substance in the liquid crystalline phase is at least 20 mg/g.

11. A composition according to any of claims 3-5 further comprising a structurant.

12. A composition according to any of the preceding claims, wherein the second substance is an amphiphilic substance such as a polar lipid, an emulsifier or a surfactant.

13. A composition according to any of the preceding claims, wherein the second substance is a fatty acid ester.

14. A composition according to any of the preceding claims, wherein the fatty acid moiety or moieties of the fatty acid ester is/are saturated or unsaturated and each have a carbon atom number from C_6 to C_{26}.

15. A composition according to claim 14, wherein the fatty acid moiety or moieties is/are a moiety or moieties of a saturated fatty acid selected from the group consisting of caproic acid, caprylic acid, capric acid, lauric acid, myristic acid, palmitic acid, stearic acid, arachidic acid, and behenic acid.

16. A composition according to claim 14, wherein the fatty acid moiety or moieties of the fatty acid component is/are unsaturated.

17. A composition according to claim 16, wherein the fatty acid moiety or moieties is/are selected from the group consisting of palmitoleic acid, oleic acid, linoleic acid, linolenic acid, and arachidonic acid.

18. A composition according to any of claims 13-17, wherein the fatty acid ester is selected from the group consisting of fatty acid esters, in particular partial fatty acid esters, of polyhydric alcohols, fatty acid esters of hydroxycarboxylic acids, fatty acid esters of monosaccharides, fatty acid esters of glycerylphosphate derivatives, fatty acid esters of glycerylsulfate derivatives, and mixtures thereof.

19. A composition according to claim 18, wherein the polyhydric alcohol is selected from the group consisting of glycerol, 1,2-propanediol, 1,3-propanediol, diacylgalactosylglycerol, diacyldigalactosylglycerol, erythritol, xylitol, adonitol, arabitol, mannitol, and sorbitol.

20. A composition according to claim 19, wherein the fatty acid ester is selected from the group consisting of glycerylmonooleate, glycerylmonolinoleate, glycerylmonolinolenate, and mixtures thereof.

21. A composition according to claim 18, wherein the hydroxycarboxylic acid is selected from the group consisting of malic acid, tartaric acid, citric acid, and lactic acid.

22. A composition according to claim 18, wherein the fatty acid ester is a fatty acid monoester of citric acid.

23. A composition according to claim 18, wherein the monosaccharide is selected from the group consisting of glucose, mannose, fructose, threose, gulose, arabinose, ribose, erythrose, xylose, galactose, sorbose, altrose, tallose, idose, rhamnose, and allose.

24. A composition according to claim 23, wherein the fatty acid ester is a fatty acid monoester of a monosaccharide selected from the group consisting of sorbose, galactose, ribose, and rhamnose.

25. A composition according to claim 18, wherein the glycerylphosphate derivative is a phospholipid selected from the group consisting of phosphatidic acid, phosphatidylserine, phosphatidylethanolamine, phosphatidylcholine, phosphatidylglycerol, phosphatidylinositole, and diphosphatidylglycerol.

26. A composition according to claim 18, wherein the fatty acid ester is a fatty acid ester of a glycerylphosphate derivative or a glycerylsulfate derivative, and the fatty acid component is selected from the group consisting of lauric acid, myristic acid, palmitic acid, stearic acid, oleic acid, linoleic acid, linolenic acid, and behenic acid.

27. A composition according to claim 26, wherein the fatty acid ester is selected from the group consisting of dioleyol phosphatidylcholine, dilauryl phosphatidylcholine, dimyristyl phosphatidylcholine, dipalmitoyl phosphatidylcholine, distearoyl phosphatidylcholine, dibehenoyl phosphatidylcholine, dimyristyl phosphatidylethanolamine, dipalmitoyl phosphatidylethanolamine, dioleyl phosphatidylglycerol, dilauryl phosphatidylglycerol, dimyristoyl phosphatidylglycerol, dipalmitoyl phosphatidylglycerol, distearoyl phosphatidylglycerol, dipalmitoyl phosphatic acid and mixtures thereof.

28. A composition according to claim 18, wherein the fatty acid ester is glycerylmonooleate or glycerylmonolinoleate

29. A composition according to claim 28, wherein the fatty acid ester is glycerylmonooleate.

30. A composition according to claim 29, wherein the glycerylmonooleate product contained in the composition contains at the most 4% of saturated monoglyceride.

31. A composition according to claim 29, wherein the glycerolmonooleate product contained in the composition contains at least 88% such as at least 89%, at least 90%, at least 91%, in particular at least 92% of glycerylmonooleate.

32. A composition according to any of claims 1-5, which contains at least 10% by weight, calculated on the composition, of the second substance.

33. A composition according to claim 1 or 2, which contains at least 15% by weight such as, e.g., at least 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, or 70% by weight, calculated on the composition, of the second substance.

34. A composition according to claim 1 or 2, wherein the concentration of the second substance in the composition is in a range corresponding to from about 10% to about 90% such as, e.g. about 15%-85%, about 20%-80%, about 25%-75%, about 25%-70%, about 25%-65%, about 25%-60%, about 25%-55%, about 30%-50%, about 35%-55%, about 30%-45% or about 30%-40% by weight based on the total composition.

35. A composition according to any of claims 1-5, wherein the concentration of the second substance in the composition is at the most about 60% such as, e.g. at the most about 55%, about 50%, about 45%, about 40%, about 35%, about 30%, about 25%, about 20%, about 15% or 10% by weight based on the total composition.

36. A composition according to any of claims 1-2, 6-35, wherein the structurant is an amphiphilic substance having a molecular weight of at the most 2000.

37. A composition according to any of claims 1-2, 6-35, wherein the structurant is an emulsifier or a polar lipid, an emulsifier or a surfactant.

38. A composition according to any of claims 1-2, 6-37, wherein the structurant has a saturated or unsaturated, branched or unbranched, substituted or unsubstituted C_6-C_{26}-alkyl chain.

39. A composition according to any of claims 1-2, 6-38, wherein the structurant is a compound which contains a polyethylene group.

40. A composition according to any of claims 1-2, 6-37, wherein the structurant has a solubility in the second substance of at least 15%, such as at least 20% or 25% by weight at 60°C.

41. A composition according to any of claims 1-2, 6-35, wherein the structurant is a substance which - together with the second substance and a liquid medium - is capable of forming a cubic liquid crystalline phase.

42. A composition according to any of claims 1-2, 6-35, wherein the structurant is a substance which - in a two component system of the structurant as a first component and water as a second component - is capable of forming a non-cubic liquid crystalline phase.

43. A composition according to claim 42, wherein - in a two component system of the structurant and water - the structurant does not form a cubic liquid crystalline phase at a temperature of between 20-40°C.

44. A composition according to any of claims 1-2, 6-35, wherein the composition comprises at least one structurant.

45. A composition according to any of claims 1-2, 6-35, wherein the composition comprises a combination of at least two structurants.

46. A composition according to any of claims 1-2, 6-35, wherein the structurant is a phospholipid selected from the group consisting of phosphatidic acid, phosphatidylserine, phosphatidylethanolamine, phosphatidylcholine, phosphatidylglycerol, phosphatidylinositole, and diphosphatidylglycerol.

47. A composition according to any of claims 1-2, 6-35, wherein the structurant is a fatty acid ester of a glycerylphosphate derivative or a glycerylsulfate derivative, and the fatty acid component is selected from the group consisting of lauric acid, myristic acid, palmitic acid, stearic acid, oleic acid, linoleic acid, linolenic acid, and behenic acid.

48. A composition according to claim 47, wherein the fatty acid ester is selected from the group consisting of dioleyol phosphatidylcholine, dilauryl phosphatidylcholine, dimyristyl phosphatidylcholine, dipalmitoyl phosphatidylcholine, distearoyl phosphatidylcholine, dibehenoyl phosphatidylcholine, dimyristyl phosphatidylethanolamine, dipalmitoyl

phosphatidylethanolamine, dioleyl phosphatidylglycerol, dilauryl phosphatidylglycerol, dimyristoyl phosphatidylglycerol, dipalmitoyl phosphatidylglycerol, distearoyl phosphatidylglycerol, dipalmitoyl phosphatic acid and mixtures thereof.

49. A composition according to claim 45, wherein the structurant is a phosphatidylcholine selected from the group consisting of Epikuron 200, Epikuron 145, Lipoid S100 or Lipoid S75.

50. A composition according to any of claims 1-2, 11, wherein the concentration of the structurant is in a range of from about 1% to about 60% such as, e.g., from about 5% to about 55%, from about 5% to about 50%, from about 5% to about 45%, from about 7.5% to about 40%, or from about 10% to about 35% by weight based on the total weight of the composition.

51. A composition according to any of claims 1-2, 11, wherein the structurant is a tocopherol selected from the group consisting of β-tocopherols, sorbitan esters of tocopherols and fatty acid esters of tocopherols, d-α-tocopherol, d,l-α-tocopherol, d-α-tocopherol acetate, d,l-α-tocopherol acetate, d-α-tocopherol succinate, d,l-α-tocopherol succinate, d-α-tocopherol nicotinate, d,l-α-tocopherol nicotinate, tocopherylpolyethylene glycol succinate such as d-α-tocopherylpolyethylene glycol succinate or d,l-α-tocopherylpolyethylene glycol succinate, and derivatives and analogues thereof.

52. A composition according to claim 51, wherein the structurant is a tocopherylpolyethylene glycol succinate selected from the group consisting of
d-α-tocopherylpolyethylene glycol 200 succinate,
d,l-α-tocopherylpolyethylene glycol 200 succinate,
d-α-tocopherylpolyethylene glycol 300 succinate,
d,l-α-tocopherylpolyethylene glycol 300 succinate,
d-α-tocopherylpolyethylene glycol 400 succinate,
d,l-α-tocopherylpolyethylene glycol 400 succinate,
d-α-tocopherylpolyethylene glycol 500 succinate,
d,l-α-tocopherylpolyethylene glycol 500 succinate,
d-α-tocopherylpolyethylene glycol 600 succinate,
d,l-α-tocopherylpolyethylene glycol 600 succinate,
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d-α-tocopherylpolyethylene glycol 800 succinate,
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d-α-tocopherylpolyethylene glycol 800 succinate,
d,l-α-tocopherylpolyethylene glycol 800 succinate,

d-α-tocopherylpolyethylene glycol 900 succinate,
d,l-α-tocopherylpolyethylene glycol 900 succinate,
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d-α-tocopherylpolyethylene glycol 1500 succinate,
d,l-α-tocopherylpolyethylene glycol 1500 succinate,
d-α-tocopherylpolyethylene glycol 1600 succinate,
d,l-α-tocopherylpolyethylene glycol 1600 succinate,
d-α-tocopherylpolyethylene glycol 1700 succinate and
d,l-α-tocopherylpolyethylene glycol 1700 succinate.

53. A composition according to claim 52, wherein the tocopherylpolyethylene glycol succinate is d-α-tocopherylpolyethylene glycol 1000 succinate (vitamin E TPGS) or d,l-α-tocopherylpolyethylene glycol 1000 succinate.

54. A composition according to any of claims 51-53, wherein the concentration of the tocopherol is at the most about 30% such as at the most about 25%, 20%, 15%, 10%, 5%, 2.5% or 1% by weight based on the total weight of the composition.

55. A composition according to any of claims 1-2, 6-54, wherein the structurant is a combination of vitamin E TPGS and a phosphatidylcholine containing product such as, e.g., Epikuron 200.

56. A composition according to claim 55, wherein the concentration of vitamin E TPGS is in a range corresponding to from about 1% to about 30% by weight and the concentration of Epikuron 200 is in a range corresponding to from about 2.5% to about 40% by weight based on the total composition.

57. A composition according to any of claims 1-2, 6-56, wherein the concentration of the structurant(s) in the composition is at least about 1% by weight such as, e.g., at least about 5%, about 10%, about 15%, about 20%, about 25% or about 30% by weight based on the total weight of the composition.

58. A composition according to any of claims 1-2, 6-57, wherein the concentration of the structurant(s) in the composition is at the most about 45% by weight such as, e.g., at the most least about 40% or about 35% by weight based on the total weight of the composition.

59. A composition according to any of 1-2, 6-58, wherein the total concentration of the second substance and the structurant(s) is at least 50% by weight based on the total composition.

60. A composition according to any of claims 1-2, 6-59, wherein the liquid crystalline phase has been generated by a liquid medium present in the composition and wherein the total concentration of the second substance and the structurant(s) is at least 50% such as at least 55%, 60%, 65%, 70% or 75% by weight based on the total composition.

61. A composition according to any of claims 1-2, 6-59, wherein the composition is in a precursor form and wherein the total concentration of the second substance and the structurant(s) is at least 50% such as at least 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or 99.5% by weight based on the total composition.

62. A composition according to any of the preceding claims, wherein a liquid medium iv) is present in the composition.

63. A composition according to claim 62, wherein the liquid medium is present in a concentration of at least about 0.5% by weight, such as at least about 1% by weight, calculated on the total composition.

64. A composition according to claim 62, wherein the liquid medium is present in a concentration of at least about 2% such as at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25% or at least about 30% by weight, calculated on the total composition.

65. A composition according to claim 62, wherein the liquid medium is present in a concentration of 20%-50% such as, e.g., about 25%-35% about 25%-30% or about 30%-40% by weight, calculated on the total composition.

66. A composition according to claim 62, wherein the liquid medium is present in a concentration of 25%-40% such as, e.g, about 30%-40% or 27%-37% by weight, calculated on the total composition.

67. A composition according to any of the preceding claims, in which the liquid crystalline phase generated by the second substance and, whenever appropriate, the structurant together with a sufficient amount of a liquid medium is a cubic phase.

68. A composition to any of claims 1-2, 11, in which the liquid crystalline phase generated by the second substance and the structurant together with a liquid medium has a pH in the range of 3.0-8, such as, e.g., 3.1-8, 3.2-8, 3.3-8, 3.4-8, 3.5-8, 3.6-8, 3.7-8, 3.8-8, 3.9-8, 4.0-8, 4.1-8, 4.2-8, 4.3-8, 4.5-8, 4.75-8 or 5.0-8.

69. A composition according to claim 1 or 6,in which the second solubility of the active substance is at the most 7 mg/g, such as, e.g., at the most 5 mg/g, at the most 3 mg/g or at the most 2 mg/g.

70. A composition according to claim 1 or 6, in which the first solubility of the active substance in the liquid crystalline phase is at the most 15 mg/g such as, e.g. at the most 10 mg/g, at the most 7 mg/g or at the most 6.5 mg/g, at the most 6 mg/g, at the most 5.5 mg/g, at the most 5 mg/g, at the most 4 mg/g, at the most 3 mg/g, at the most 2 mg/g or at the most 1 mg/g at 20°C.

71. A composition according to any of the preceding claims, in which the active substance is present in a concentration above the saturation concentration at 20°C.

72. A composition according to claim 71, wherein the proportion of the active substance present which is above the saturation concentration at 20°C is at least 25% such as, e.g., at least 50%, at least 75%, at least 90%, at least 95% or at least 98% by weight of the active substance present in the composition.

73. A composition according to any of the preceding claims, wherein the active substance has a lipophilicity of at the most 100 such as at the most about 75, 50, 40, 30, 25, 10, 7.5, 5 or 2.5, expressed as the partition coefficient between octanol and 0.05M phosphate buffer, pH 7.

74. A composition according to claim 73, wherein the partition coefficient is at the most 1 such as at the most about 0.75, 0.5, 0.1, 0.075.

75. A composition according to claim 74, wherein the partition coefficient is at the most 0.05 such as at the most about 0.04.

76. A composition according to any of claims 1-72, wherein the active substance has a lipophilicity of at the most 100 such as at the most about 75, 50, 25, 10, 7.5, 5 or 2.5, expressed as the partition coefficient between octanol and an appropriate buffer having a pH corresponding either to the pH of the liquid crystalline phase or to the pH at which the active substance has its minimum solubility.

77. A composition according to claim 76, wherein the partition coefficient is at the most 1 such as at the most about 0.75, 0.5, 0.1, 0.075.

78. A composition according to claim 77, wherein the partition coefficient is at the most 0.05 such as at the most about 0.04.

79. A composition according to any of the preceding claims, wherein the release of the active substance from the liquid crystalline phase, as defined by the slope of the cumulative release in μg as a function of the square root of the release time in hours in the release experiment defined in Example 92 (in which the concentration of the substance is 5%), is at least 50 such as, e.g., at least 100, at least 200, at least 300, at least 500. at least 700 or at least 900.

80. A composition according to any of the preceding claims, which complies with the requirements of bioadhesion defined herein when tested for bioadhesion in an <u>in vivo</u> model.

81. A composition according to claim 80 which complies with the requirements for bioadhesion defined herein when tested for bioadhesion in the <u>in vivo</u> model described herein involving testing the rinsing off ability from skin.

82. A composition according to claim 80, wherein the score obtained in said test for bioadhesion is substantially of the same order of magnitude as would have been obtained for a comparative composition wherein the structurant(s) has(have) been replaced with the same amount by weight of said second substance.

83. A composition according to any of the preceding claims adapted for administration of an active substance to or through a nail or a damaged or undamaged skin or mucosal surface or for application on or at a tooth or a dental pocket of an animal such as a human.

84. A composition according to any of the preceding claims, wherein the active substance is an antiviral drug.

85. A composition according to claim 84, wherein the antiviral substance is selected from nucleosides, phosphorylated nucleosides, nucleoside analogues, nucleotide analogues, and salts, complexes and prodrugs thereof.

86. A composition according to claim 85, wherein the antiviral substance is selected from acyclovir, famciclovir, deciclovir, penciclovir, zidovudin, ganciclovir, didanosin, zalcitabin, valaciclovir, sorivudine, lobucavir, brivudine, cidofovir, n-docosanol and ISIS-2922.

87. A composition according to claim 86, wherein the antiviral substance is acyclovir.

88. A composition according to claim 87, wherein the second substance is a the fatty acid ester and a liquid medium is present in the composition.

89. A composition according to claim 88, wherein the fatty acid ester is a glycerylmonooleate product having a glycerylmonooleate content of at least 88% such as, e.g., at least about 89 or 90% by weight and a content of saturated monoglycerides of at the most 4% by weight.

90. A composition according to claim 88, wherein the content of glycerylmonooleate in the glycerylmonooleate product is at least 91% such as, e.g., at least 92% by weight.

91. A composition according to claim 88, wherein the content of saturated monoglycerides in the glycerylmonooleate product is at the most 2% by weight.

92. A composition according to claim 88, wherein the weight ratio between the glycerylmonooleate and the liquid medium is in the range between 1:0.3 and 1:2 such as between 1:0.5 and 1:1.5 such as, e.g. 1:1.

93. A composition according to claim 88, wherein the weight ratio between the combination of the glycerylmonooleate and the structurant, and the liquid medium is in the range between 60:40 and 75:25 such as between 63:37 and 73:27.

94. A composition according to any of the preceding claims, wherein Epikuron 200 and Vitamin E TPGS are present as structurant.

95. A composition according to claim 94, wherein the weight ratio between Epikuron and Vitamin E TPGS is between about 1:0.5 and 1:2 such as, e.g., between 1:0.75 and 1:1.5 such as, e.g., about 1:1.

96. A composition according to any of the preceding claims comprising glycerylmonooleate as second substance, a mixture of Epikuron 200 and Vitamin E TPGS as structurants, and water as a liquid medium.

97. A composition according to claim 96, wherein the concentration of Epikuron 200 is in a range of from 1%-25% by weight, the concentration of Vitamin E TPGS is in a range of from 1%-25% by weight, and the concentration of water is in a range of from 20%-40% by weight based on the total composition.

98. A composition according to claim 97, in which the second substance is a fatty acid ester and the composition is in a precursor form.

99. A composition according to claim 98, wherein the weight ratio between fatty acid ester and any liquid medium present in the composition is between 50:50 and 100:0 such as between 60:40 and 99:1, between 70:30 and 90:10.

100. A composition according to claim 98, wherein the weight ratio between the sum of the glycerylmonooleate and any structurant(s), and any liquid medium present in the composition is between 90:10 and 99:0.5, such as between 90:10 and 99:1.

101. A composition according to any of claims 88-100, wherein the liquid medium present in the composition is water or glycerol, or a mixture of water and glycerol.

102. A composition according to claim 101, wherein the liquid medium is water.

103. A composition according to claim 102, wherein the liquid medium is water containing glycerol in an amount of up to corresponding to a glycerol:water ratio of 2.5:1 by weight, such as up to corresponding to a glycerol:water ratio of 1.5:2 such as, e.g., a ratio of about 1:1, 0.5:1, or 0.25:1.

104. A composition according to any of the preceding claims comprising glycerylmonooleate, phosphatidylcholine and, optionally, water and the weight ratio between the content of phosphatidylcholine and glycerylmonooleate is at the most 1, such as e.g. 1:1, 1:2 or 1:4.

105. A composition according to claim 104, wherein the concentration of water in the composition is at the most 40% w/w based on the total composition.

106. A composition according to any of the preceding claims further comprising glycerol.

107. A composition according to claim 106, wherein the total concentration of glycerol and any water present is at the most 40% w/w based on the total composition.

108. A composition according to any of claims 1-2, 6-107 further comprising a pharmaceutically acceptable excipient.

109. A composition according to claim 108, wherein the pharmaceutically acceptable excipient has a solubility of less than about 15% w/w such as less than about 12.5%, about 10%, or about 7.5% in said second substance at 60°C.

110. A composition according to claim 3 or 108, wherein the pharmaceutically acceptable excipient has a solubility of less than about 15% such as less than about 10%, about 5%, about 2.5%, about 1%, or about 0.5% by weight in the liquid crystalline phase generated by the components of the composition and, if appropriate, a liquid medium at room temperature.

111. A composition according to claim 108, wherein the pharmaceutically acceptable excipient has a solubility of more than about than about 15% such as more than about 25%, 30% or 50% by weight in said second substance at 60°C.

112. A composition according to any of claims 3, 4, 108, 110, wherein the pharmaceutically acceptable excipient is an inert diluent or filler selected from the group consisting of sucrose, sorbitol, sugar, mannitol, microcrystalline cellulose, carboxymethylcellulose sodium, methylcellulose, hydroxypropyl methylcellulose, ethylcellulose, starches including potato starch, calcium carbonate, sodium chloride, lactose, calcium phosphate, calcium sulfate, sodium phosphate, and a polysaccharide such as, e.g., carmelose, a chitosan, a pectin, xanthan gum, a carrageenan, locust bean gum, acacia gum, a gelatin, an alginate, and dextrans and salts thereof.

113. A composition according to any of claims 3, 5 or 111, wherein the pharmaceutically acceptable excipient is selected from the group consisting of sorbitan esters, polysorbates, macrogols, polyethylene glycols, and propylene glycols.

114. A composition according to claim 113, wherein the concentration of the pharmaceutically acceptable excipient is at least about 5% by weight such as, e.g., about 5-10%, 10-15%, 15-20% or 20-25% by weight.

115. A composition according to any of the preceding claims further comprising a pharmaceutically acceptable additive.

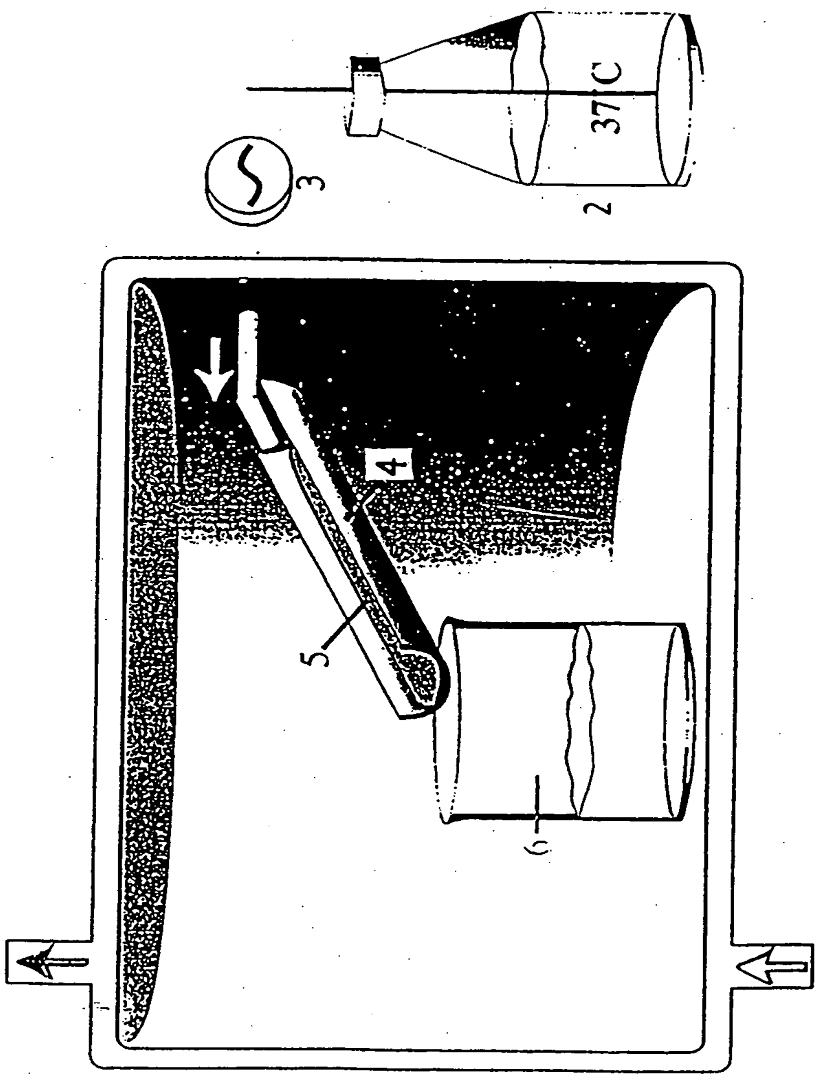
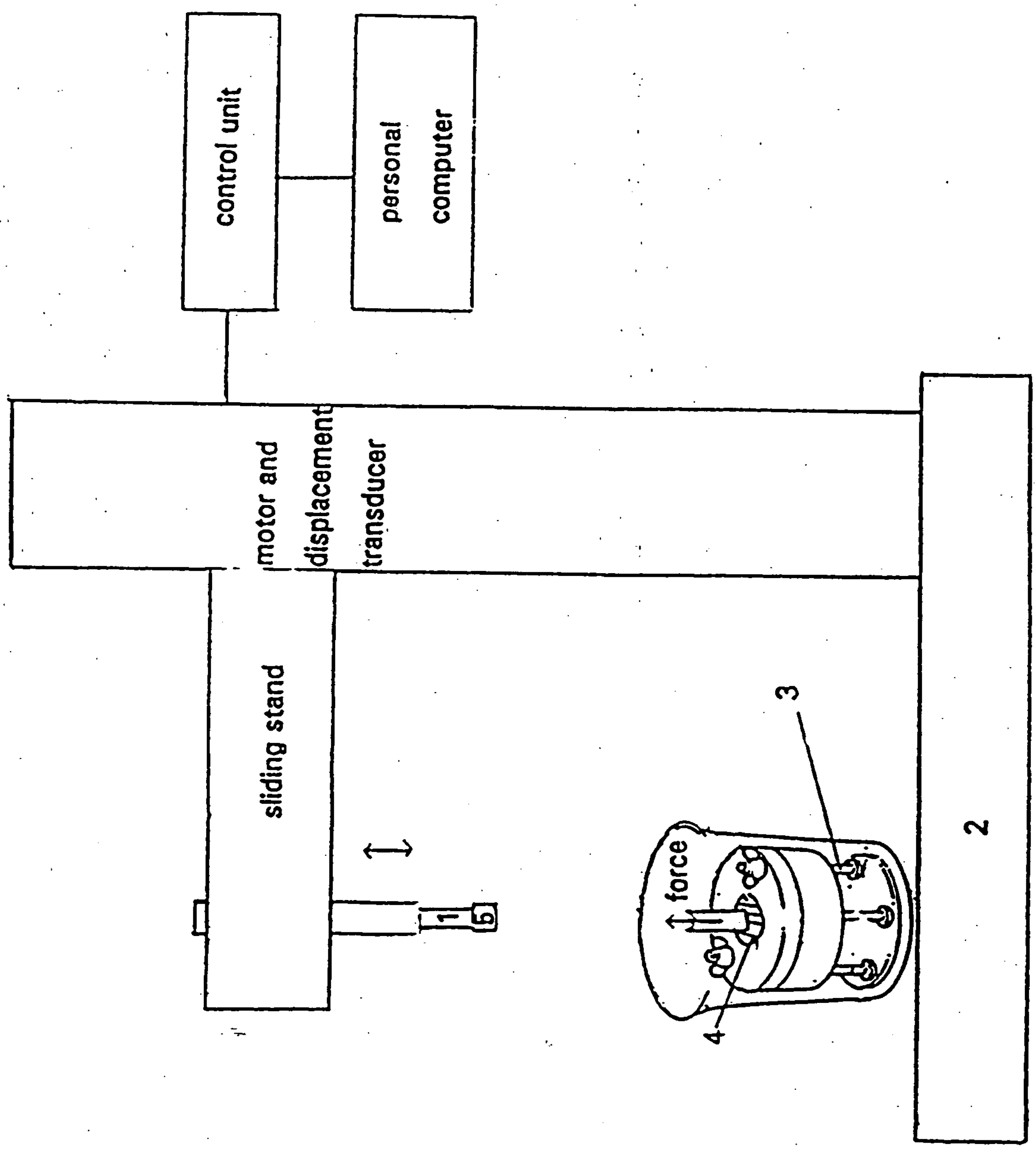


Fig. 1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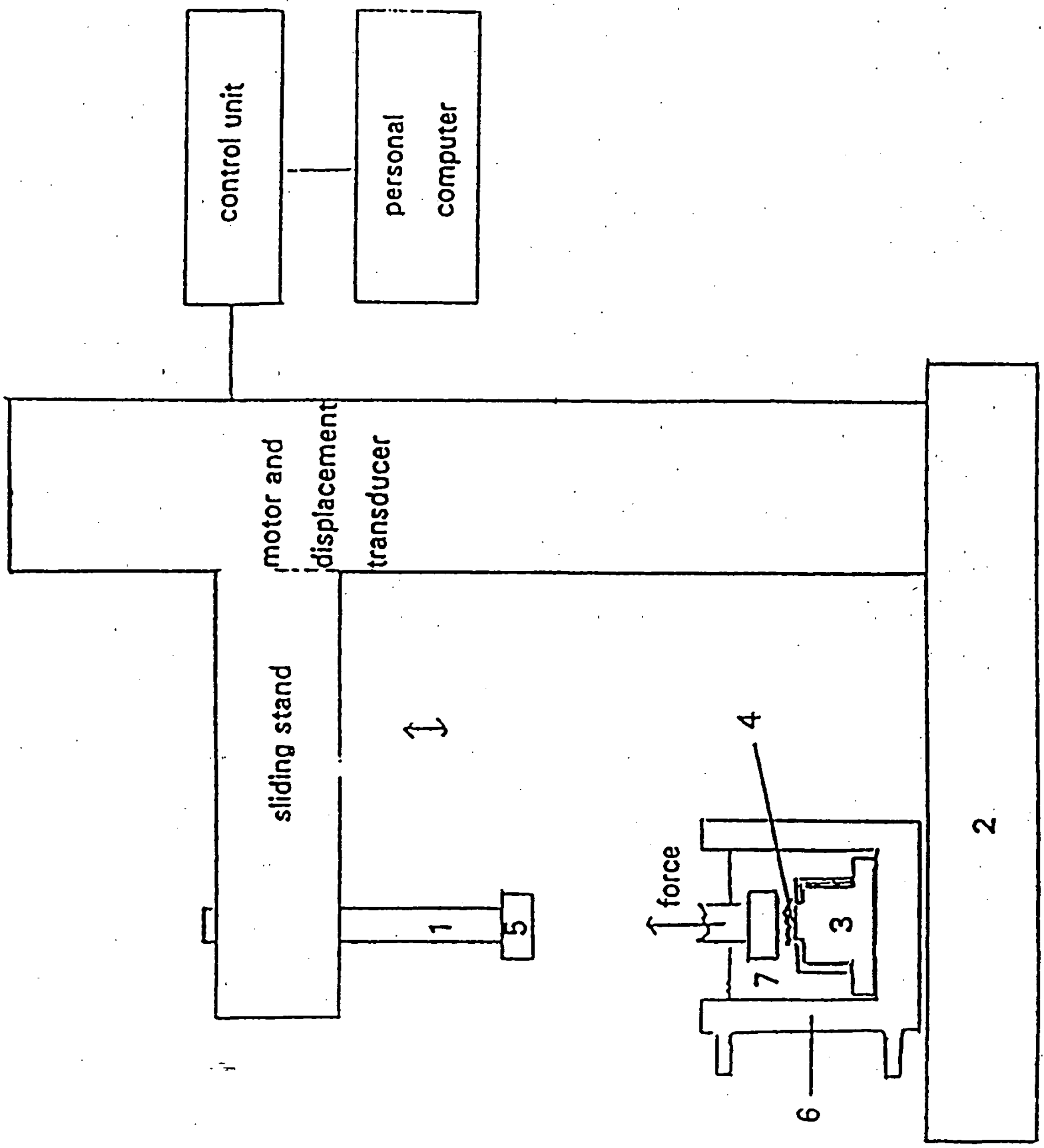
personal computer
motor and displacement transducer
sliding stand
force
1
2
3
4
5

Fig. 2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personal computer
motor and displacement transducer
sliding stand
force
1
2
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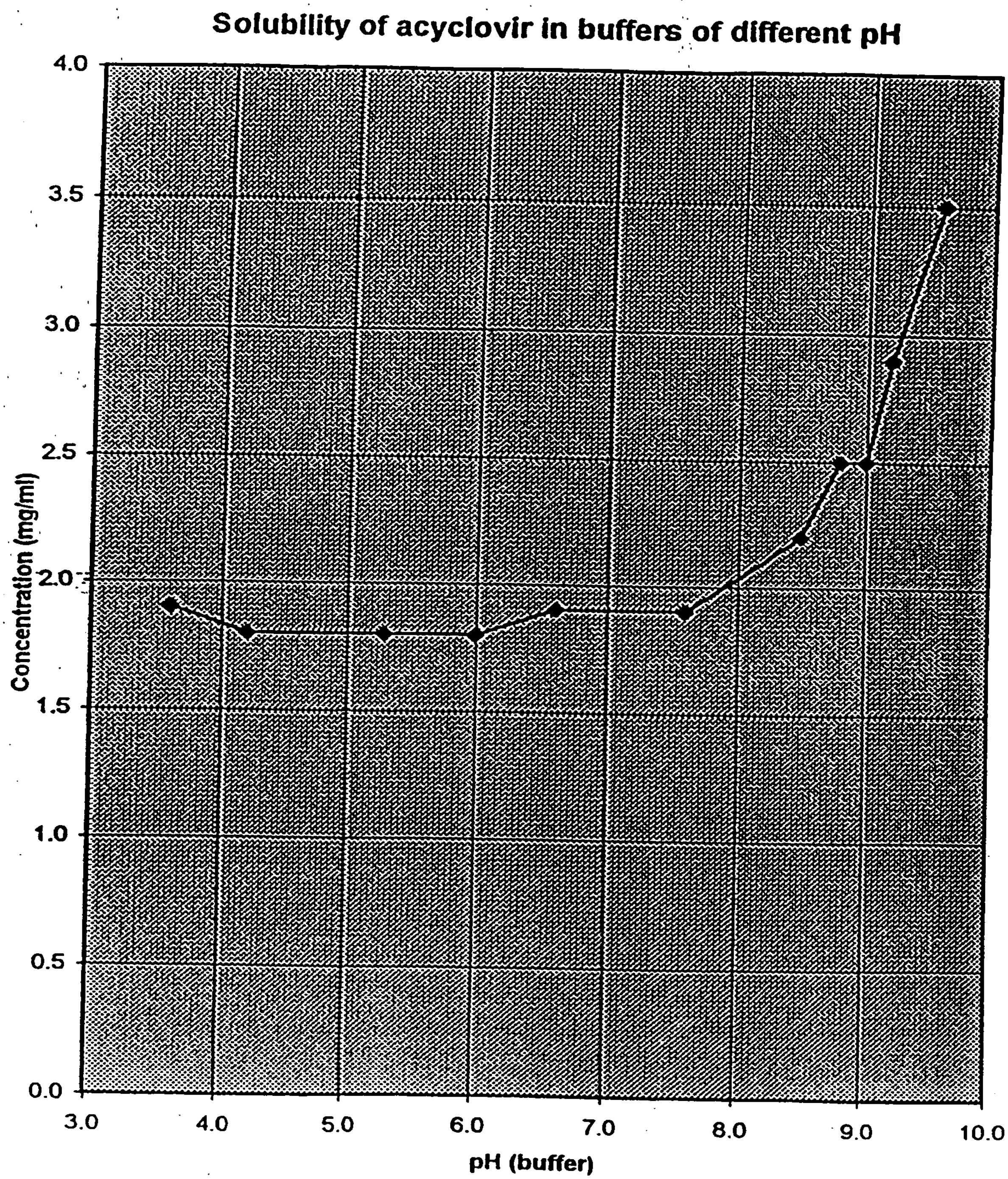
6
7

Fig. 3


Solubility of acyclovir in buffers of different pH
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3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
Concentration (mg/ml)
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4.0
5.0
6.0
7.0
8.0
9.0
10.0
pH (buffer)

Fig. 4

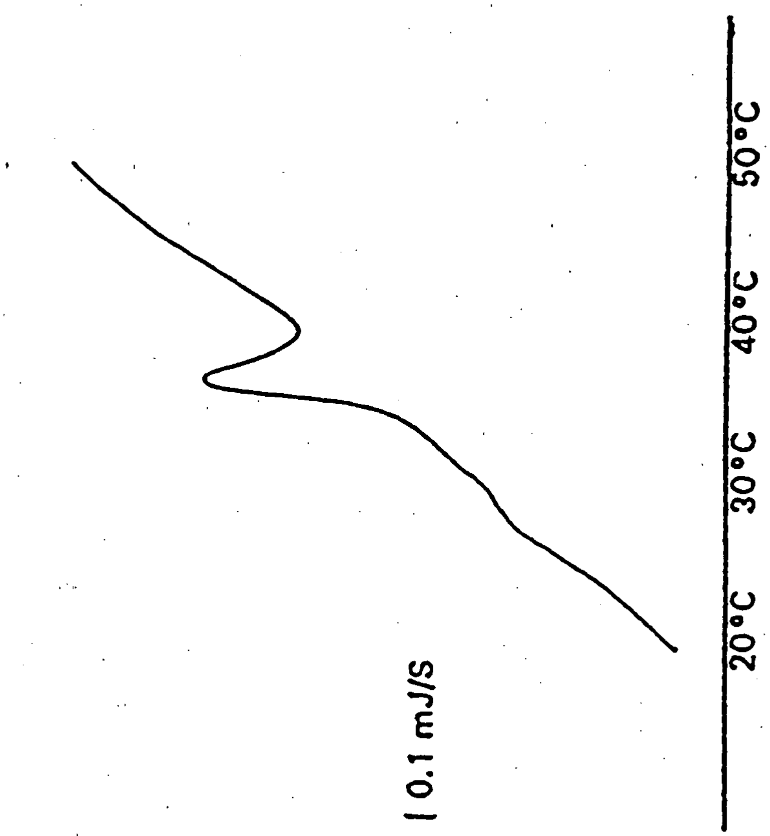

Fig. 5

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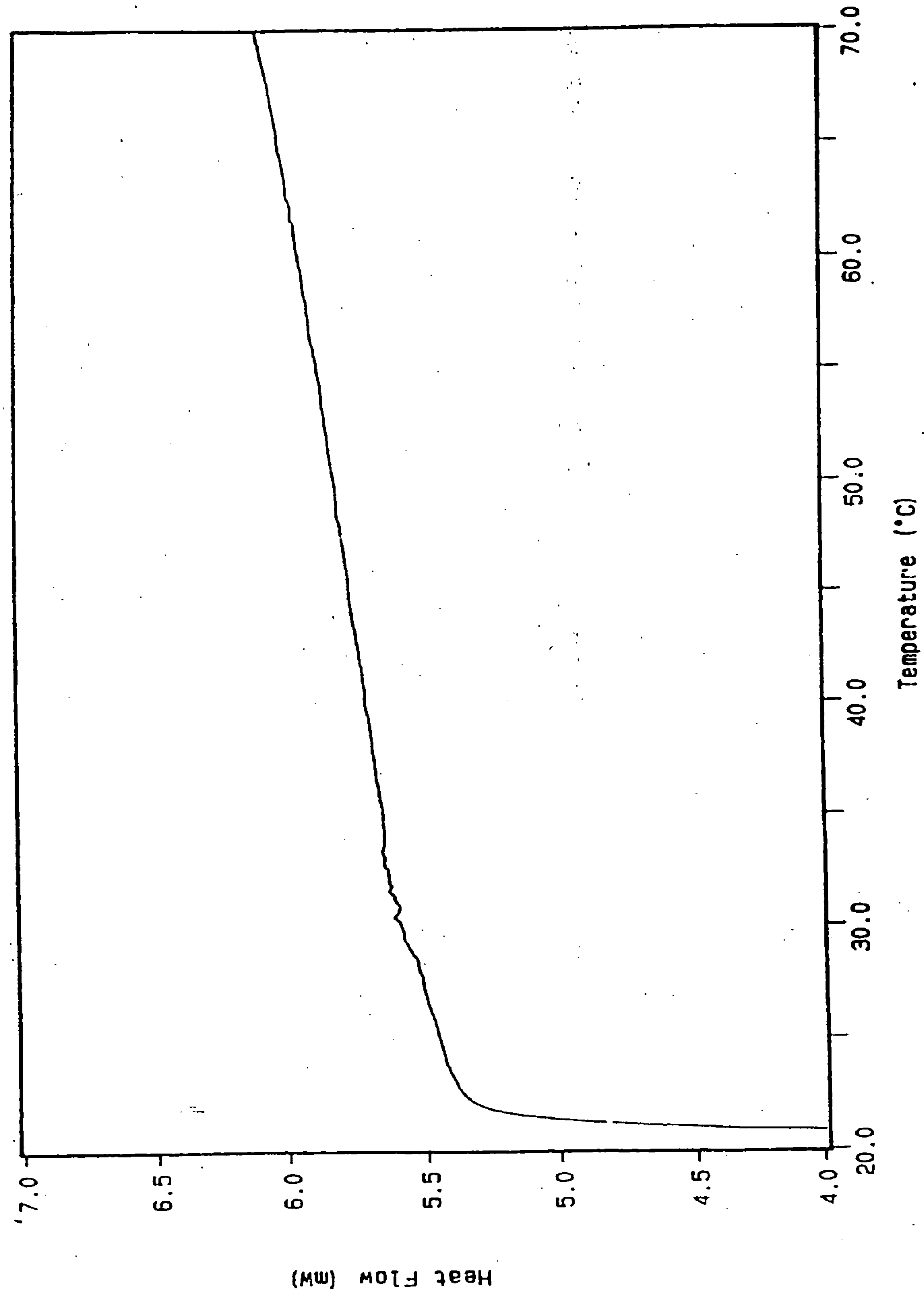
Heat Flow (mW)
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6.5
6.0
5.5
5.0
4.5
4.0
Temperature (°C)
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30.0
40.0
50.0
60.0
70.0

Fig. 6

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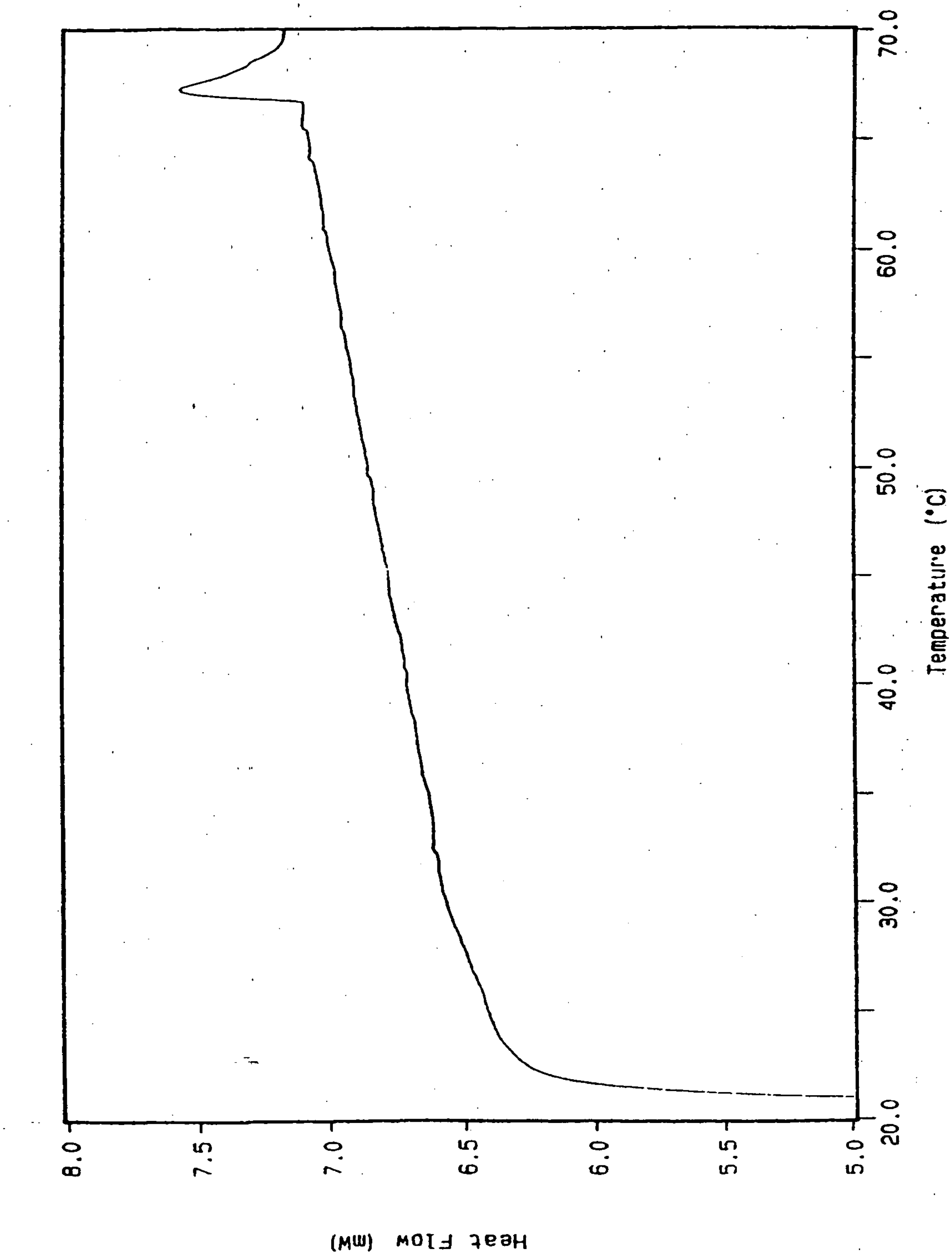

Heat Flow (mW)
8.0
7.5
7.0
6.5
6.0
5.5
5.0
Temperature (°C)
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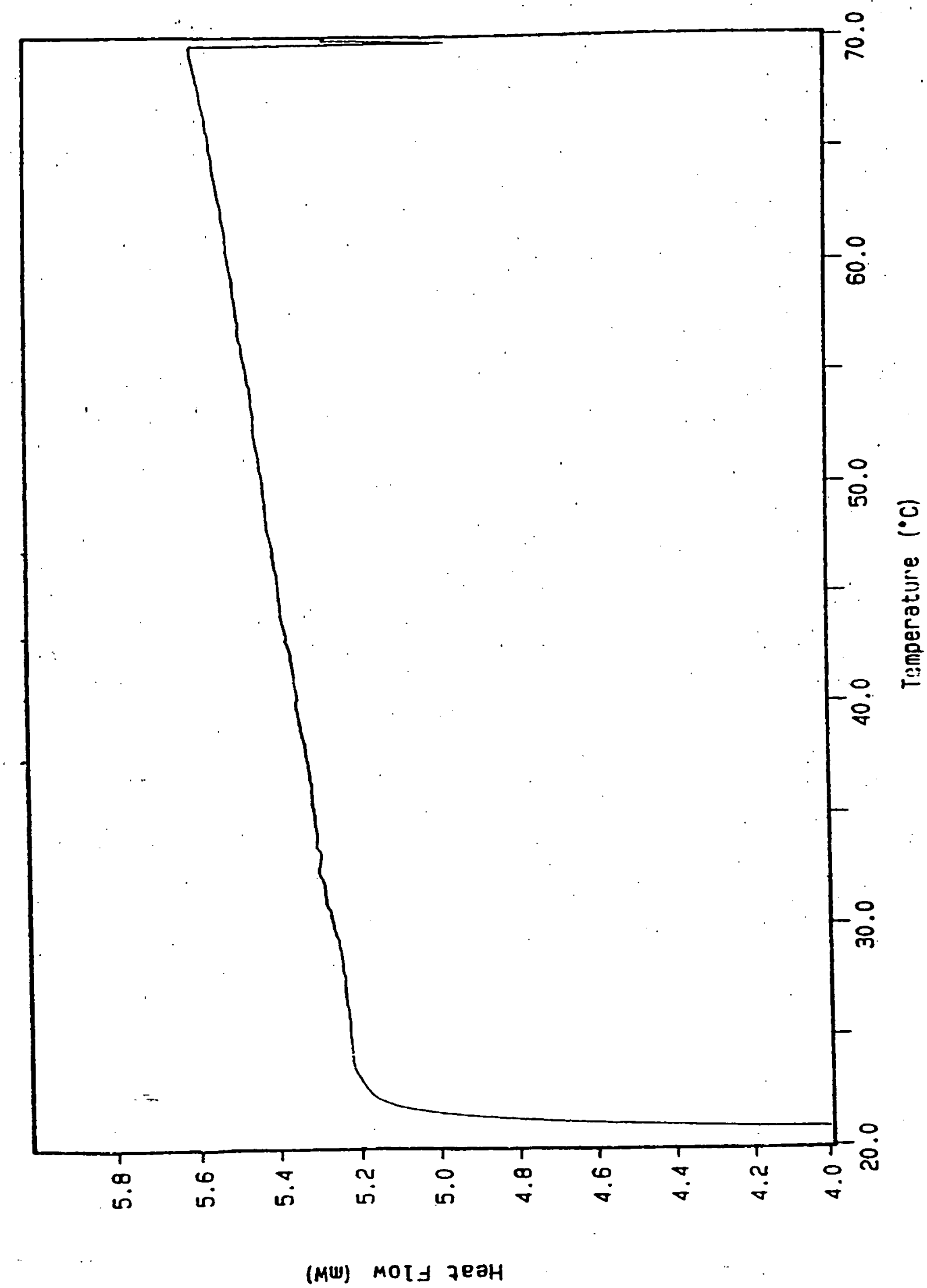
30.0
40.0
50.0
60.0
70.0

Fig. 7


Heat Flow (mW)
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5.6
5.4
5.2
5.0
4.8
4.6
4.4
4.2
4.0
Temperature (°C)
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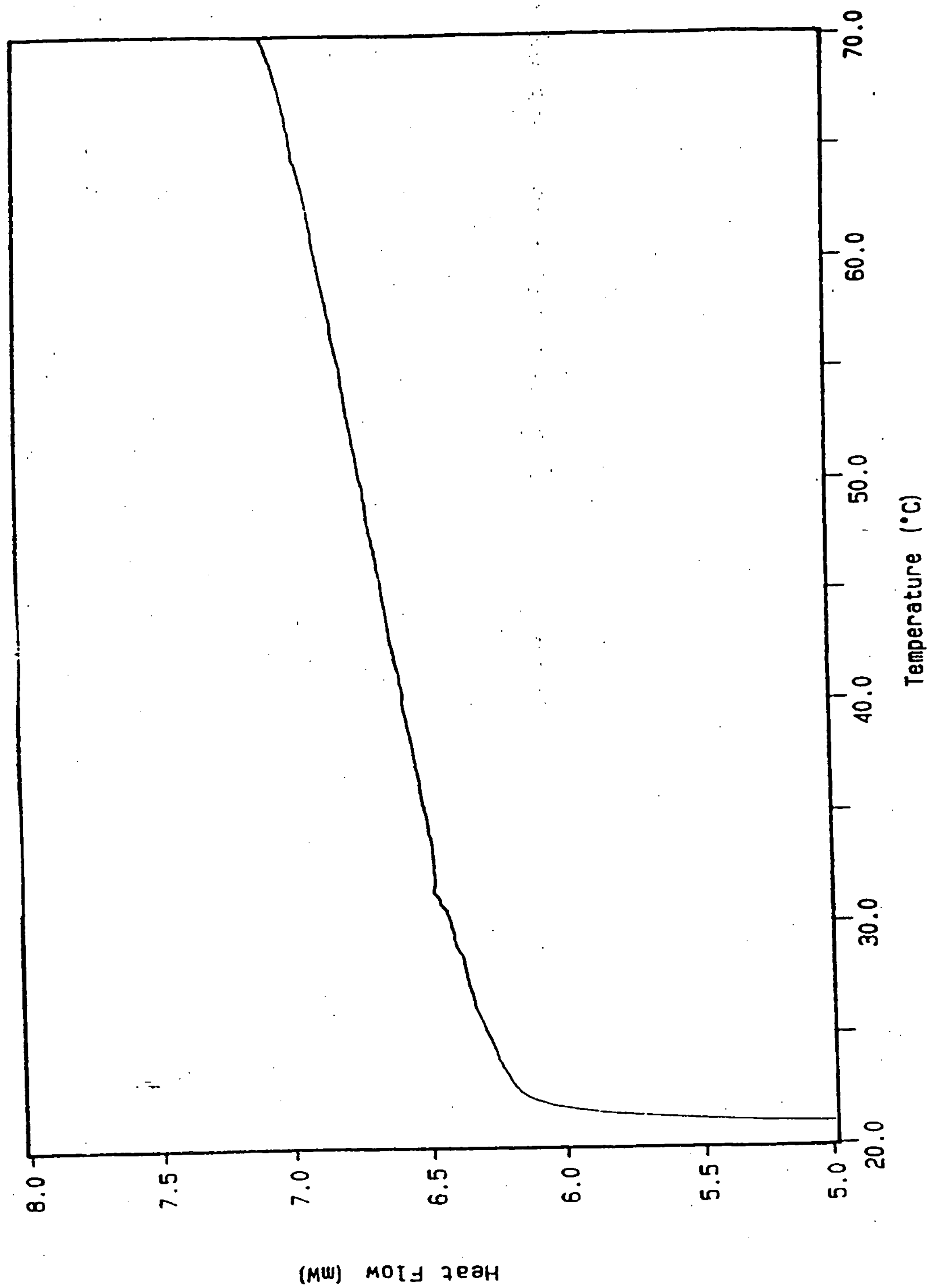
30.0
40.0
50.0
60.0
70.0

Fig. 8



Heat Flow (mW)
8.0
7.5
7.0
6.5
6.0
5.5
5.0
Temperature (°C)
20.0
30.0
40.0
50.0
60.0
70.0

Fig. 9

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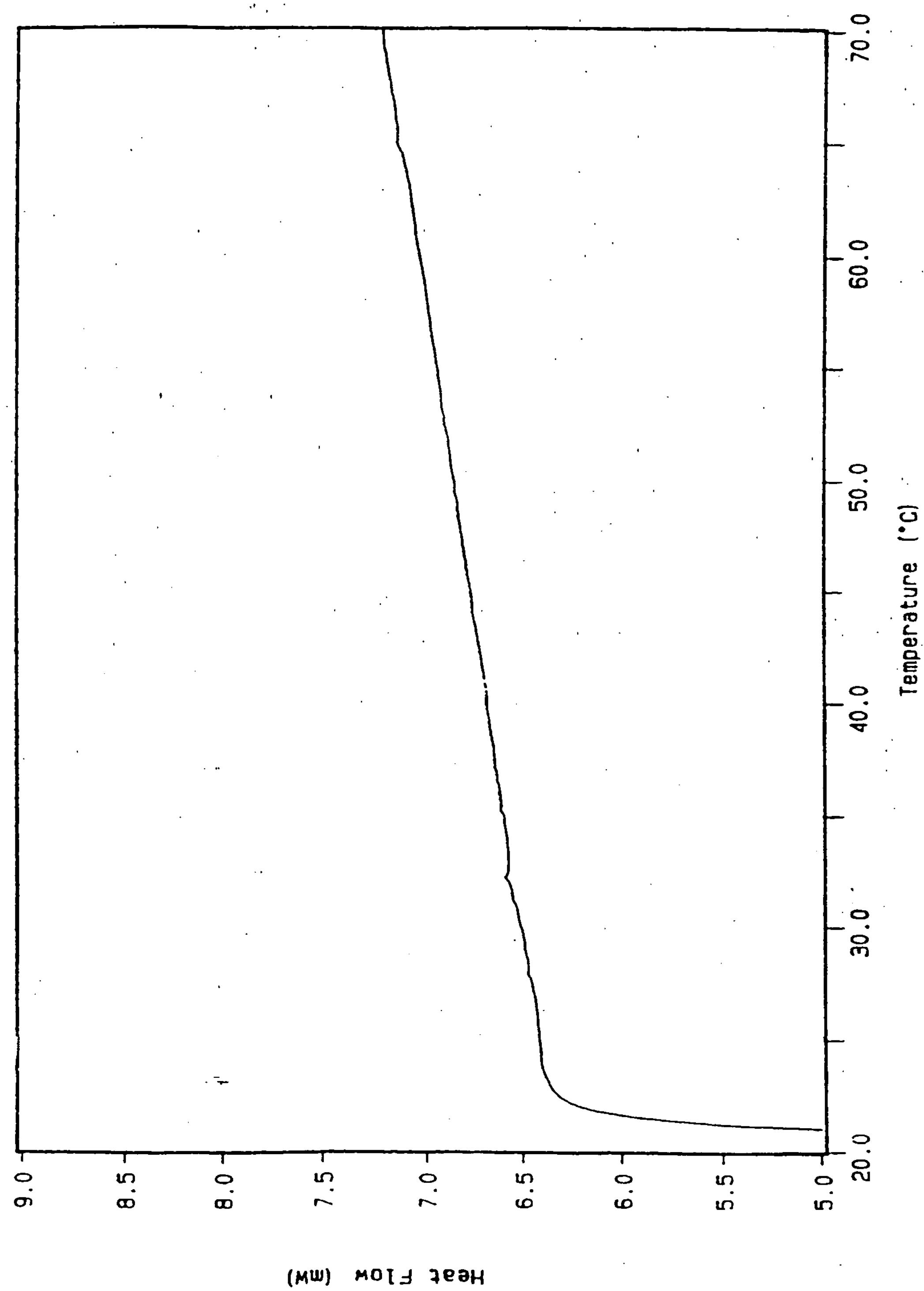
Heat Flow (mW)
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
Temperature (°C)
20.0
30.0
40.0
50.0
60.0
70.0

Fig. 10

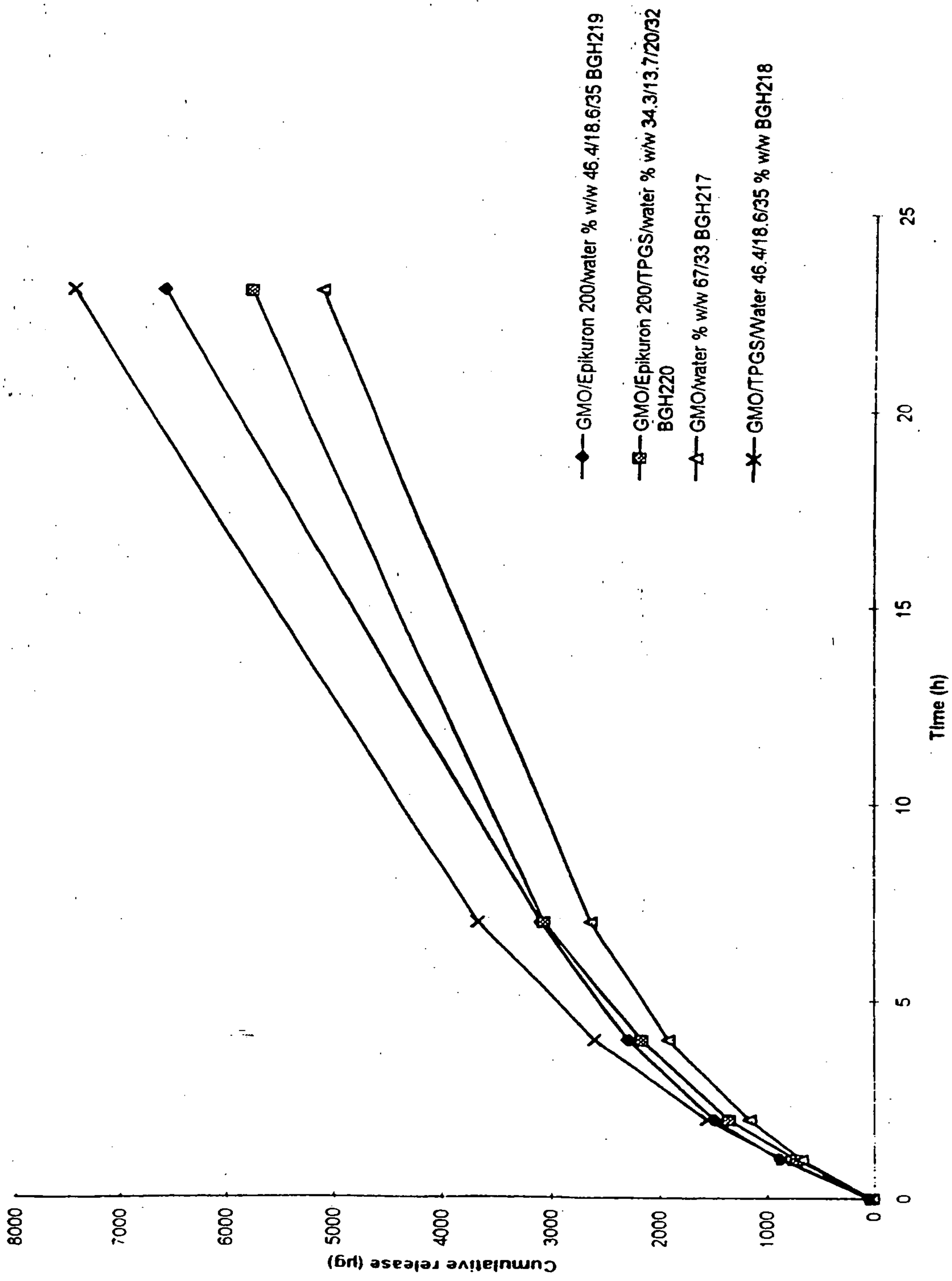
GMO/Epikuron 200/water % w/w 46.4/18.6/35 BGH219
GMO/Epikuron 200/TPGS/water % w/w 34.3/13.7/20/32 BGH220
GMO/water % w/w 67/33 BGH217
GMO/TPGS/Water 46.4/18.6/35 % w/w BGH218
Cumulative release (µg)
0
1000
2000
3000
4000
5000
6000
7000
8000
Time (h)
0
5
10
15
20
25

Fig. 11

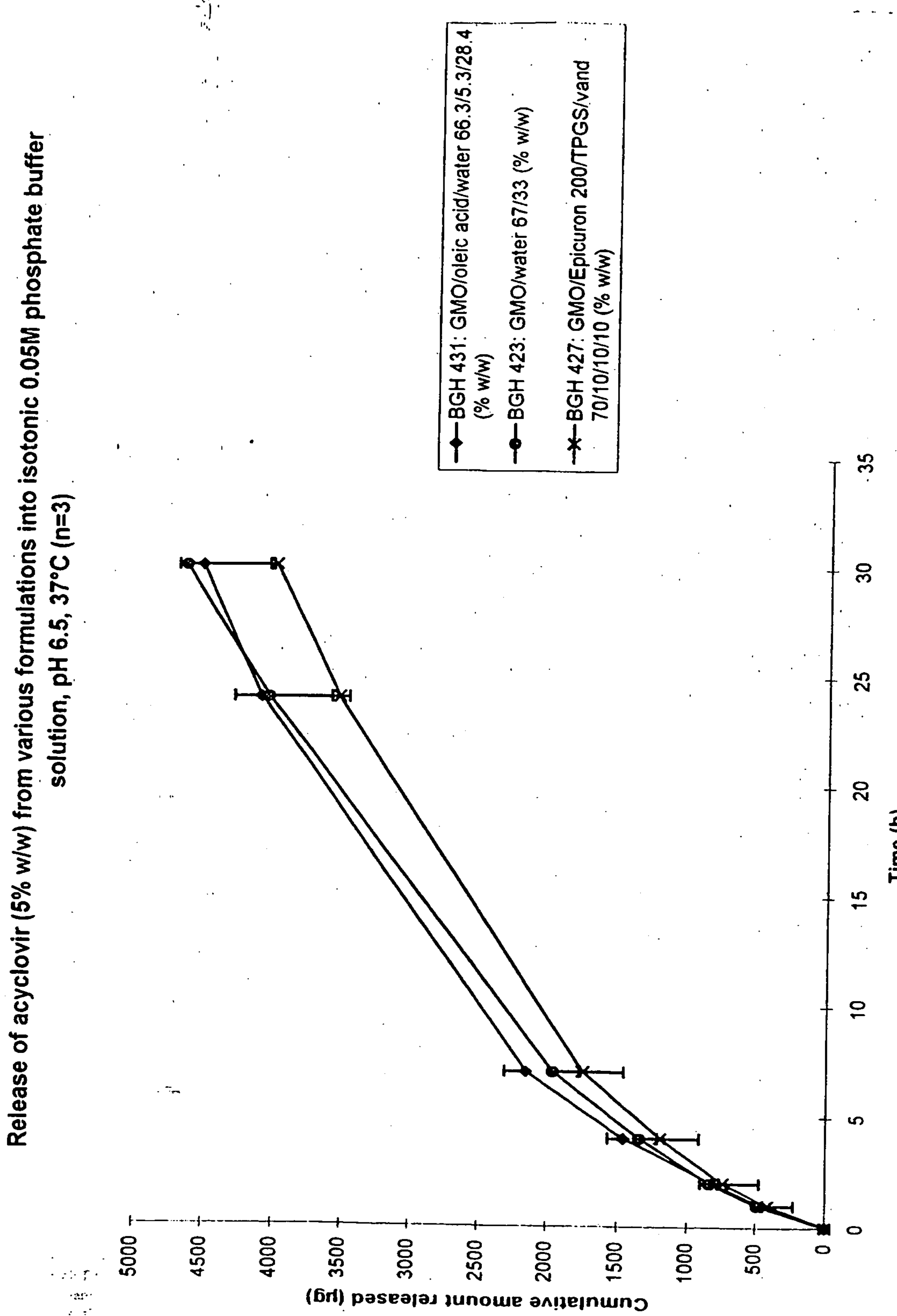
Release of acyclovir (5% w/w) from various formulations into isotonic 0.05M phosphate buffer solution, pH 6.5, 37°C (n=3)
BGH 431: GMO/oleic acid/water 66.3/5.3/28.4 (% w/w)
BGH 423: GMO/water 67/33 (% w/w)
BGH 427: GMO/Epicuron 200/TPGS/vand 70/10/10/10 (% w/w)
Cumulative amount released (µg)
0
500
1000
1500
2000
2500
3000
3500
4000
4500
5000
Time (h)
0
5
10
15
20
25
30
35

Fig. 11 a

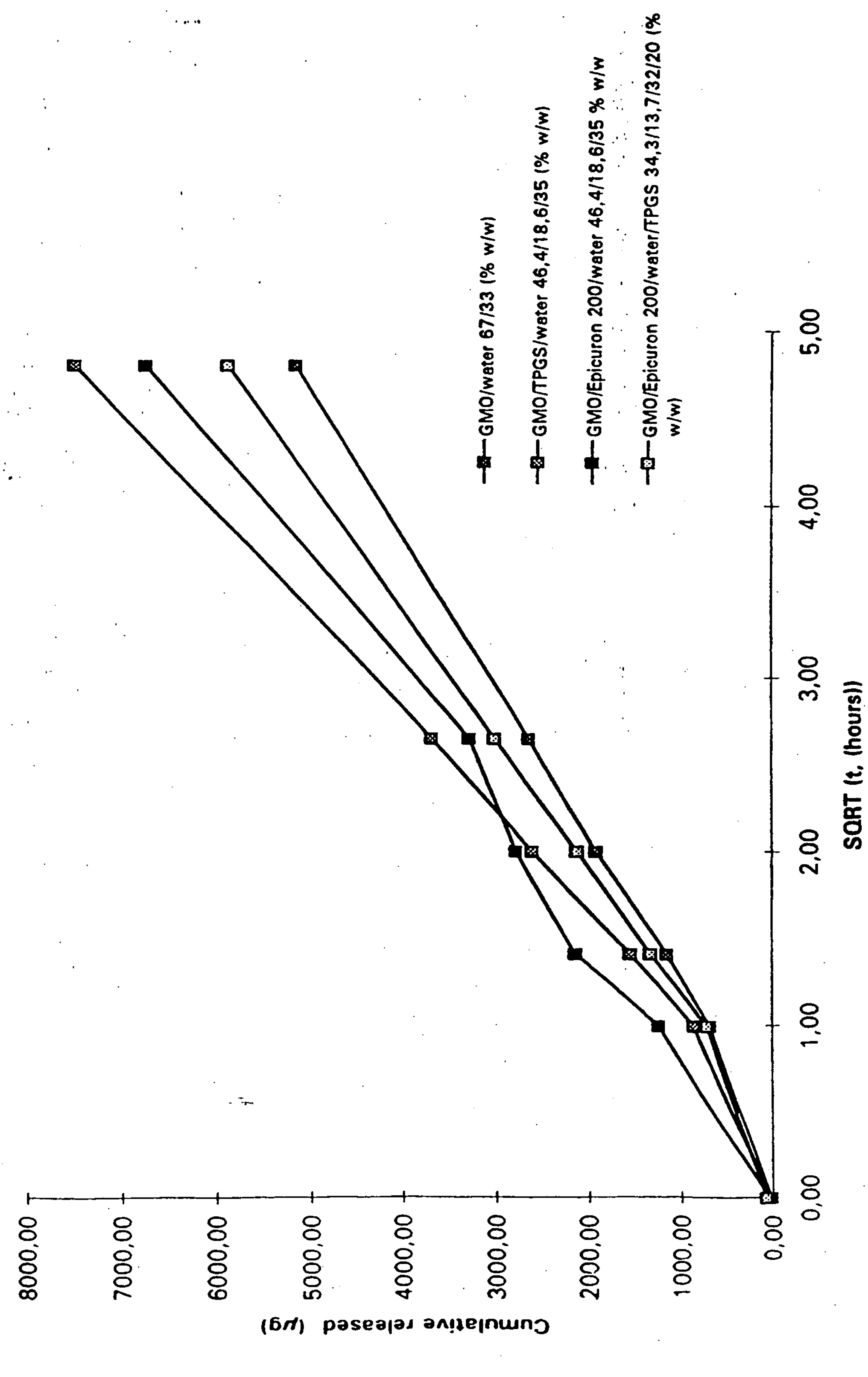
GMO/water 67/33 (% w/w)
GMO/TPGS/water 46,4/18,6/35 (% w/w)
GMO/Epicuron 200/water 46,4/18,6/35 % w/w
GMO/Epicuron 200/water/TPGS 34,3/13,7/32/20 (% w/w)
Cumulative released (µg)
8000,00
7000,00
6000,00
5000,00
4000,00
3000,00
2000,00
1000,00
0,00
SQRT (t, (hours))
0,00
1,00
2,00
3,00
4,00
5,00

Fig. 12

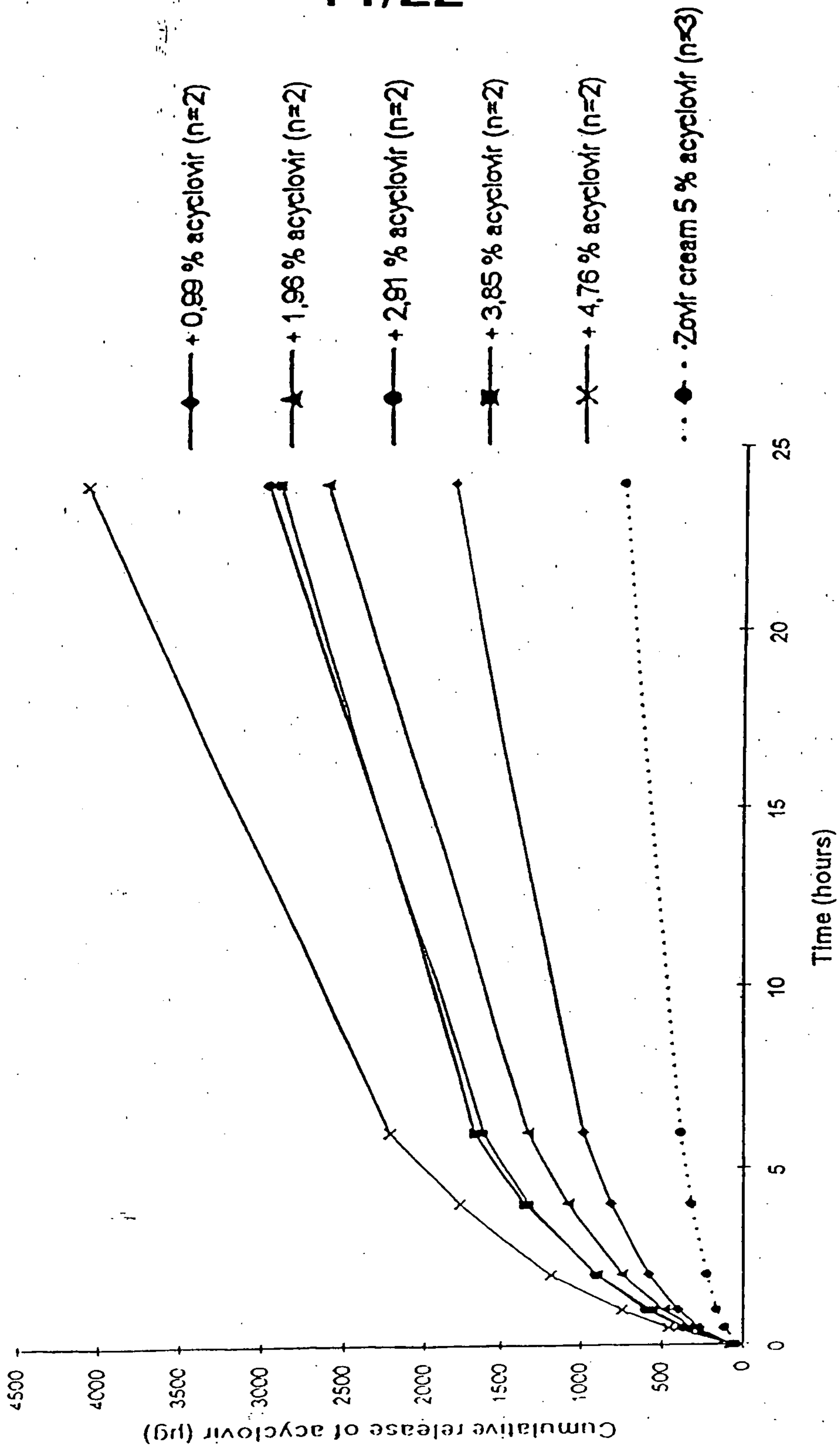
+ 0,89 % acyclovir (n=2)
+ 1,96 % acyclovir (n=2)
+ 2,91 % acyclovir (n=2)
+ 3,85 % acyclovir (n=2)
+ 4,76 % acyclovir (n=2)
Zovir cream 5 % acyclovir (n=3)
Cumulative release of acyclovir (µg)
4500
4000
3500
3000
2500
2000
1500
1000
500
0
Time (hours)
0
5
10
15
20
25

Fig. 13

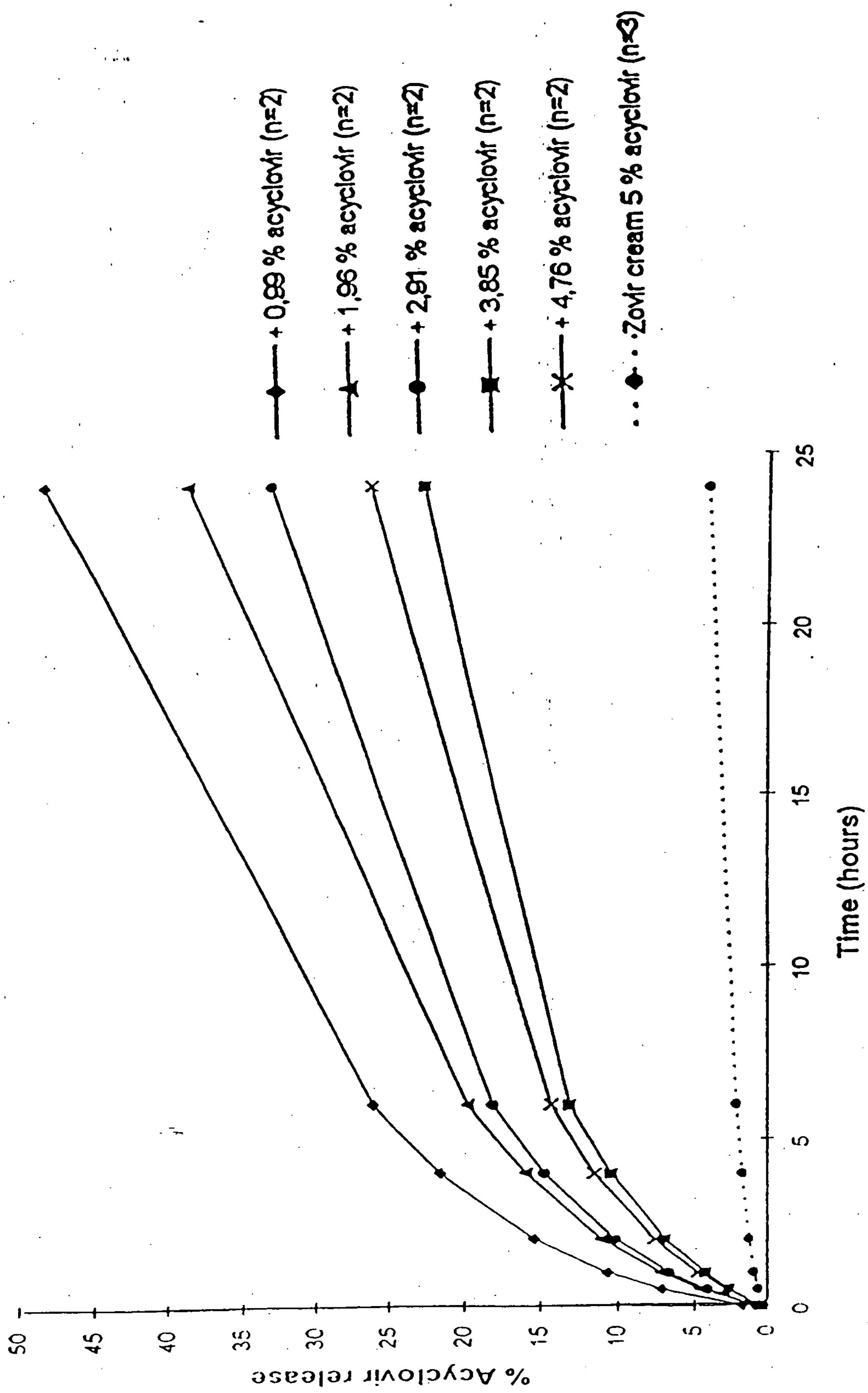
+ 0,99 % acyclovir (n=2)
+ 1,96 % acyclovir (n=2)
+ 2,91 % acyclovir (n=2)
+ 3,85 % acyclovir (n=2)
+ 4,76 % acyclovir (n=2)
Zovir cream 5 % acyclovir (n=3)
% Acyclovir release
0
5
10
15
20
25
30
35
40
45
50
Time (hours)
0
5
10
15
20
25

Fig. 14

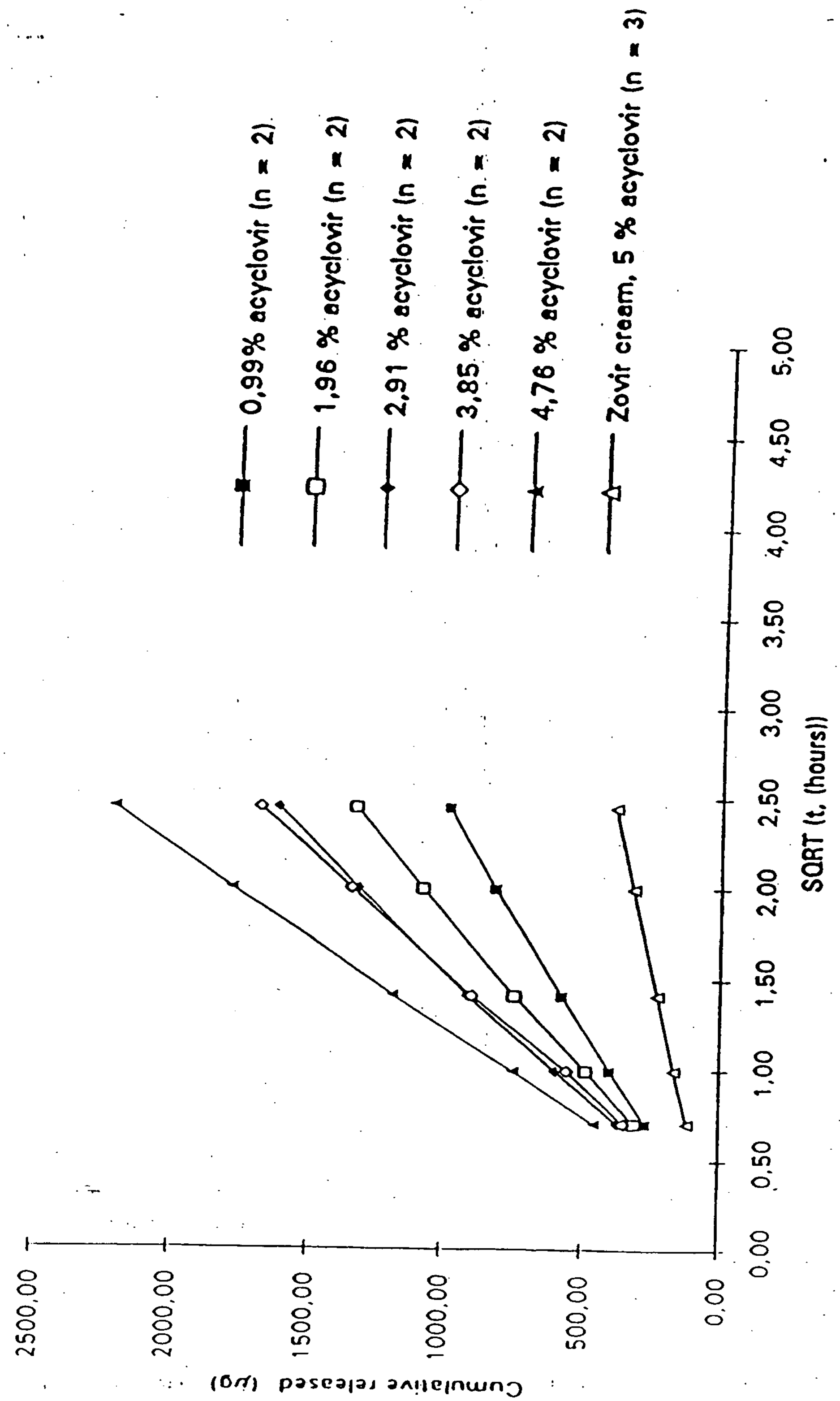
0,99% acyclovir (n = 2)
1,96 % acyclovir (n = 2)
2,91 % acyclovir (n = 2)
3,85 % acyclovir (n = 2)
4,76 % acyclovir (n = 2)
Zovir cream, 5 % acyclovir (n = 3)
Cumulative released (µg)
2500,00
2000,00
1500,00
1000,00
500,00
0,00
0,00
0,50
1,00
1,50
2,00
2,50
3,00
3,50
4,00
4,50
5,00
SQRT (t, (hours))

Fig. 15

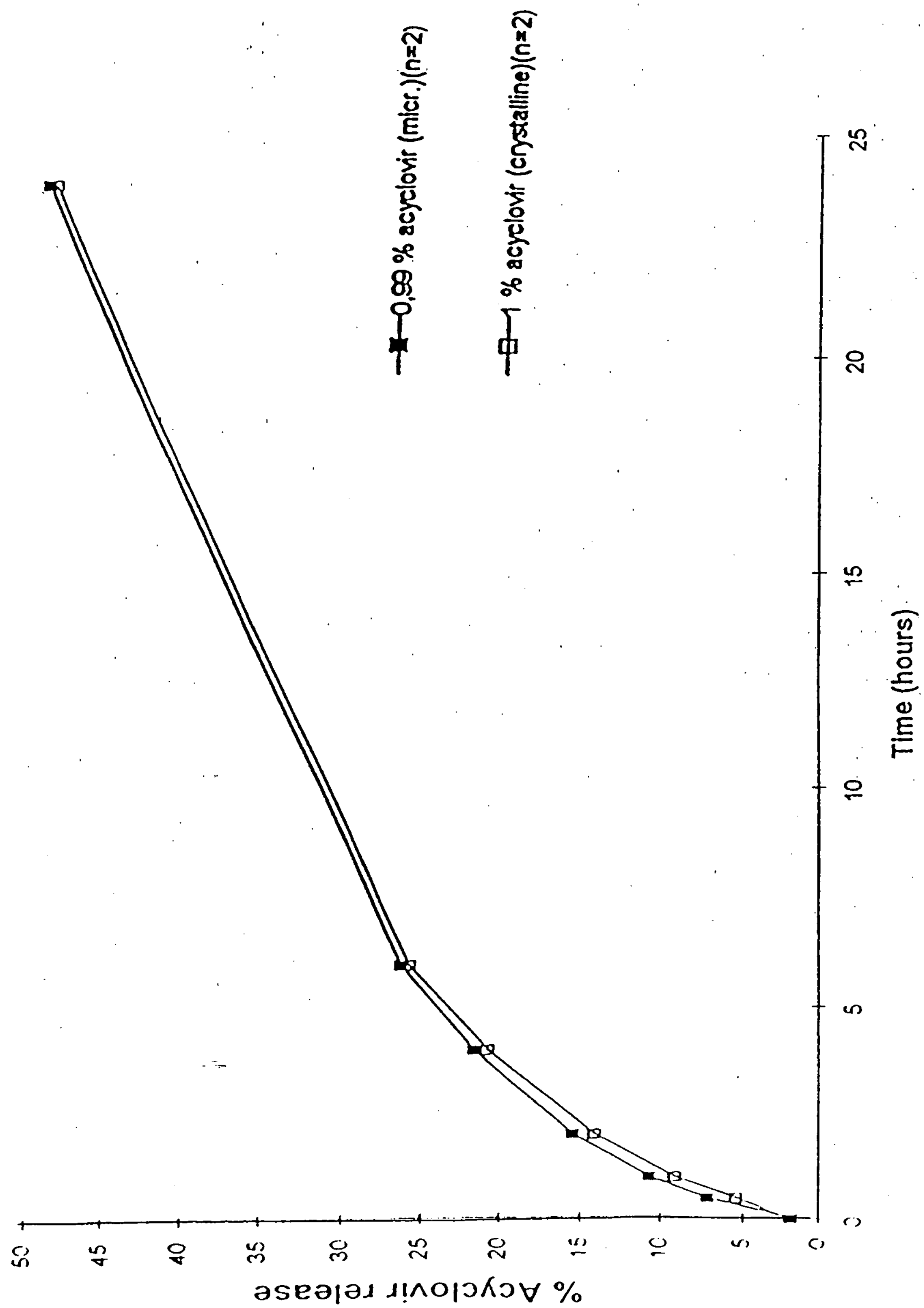
0,99 % acyclovir (micr.)(n=2)
1 % acyclovir (crystalline)(n=2)
% Acyclovir release
0
5
10
15
20
25
30
35
40
45
50
Time (hours)
0
5
10
15
20
25

Fig. 16

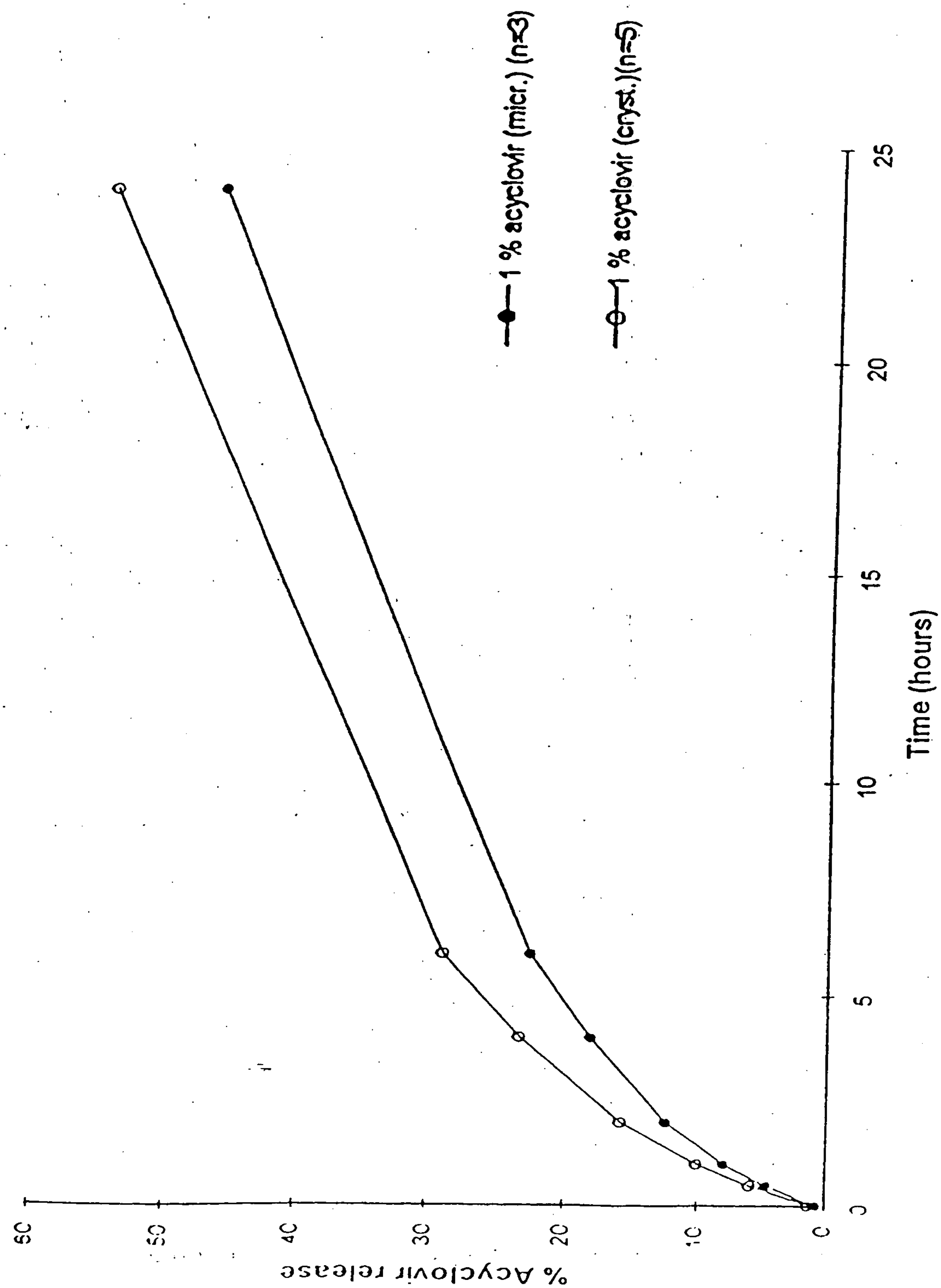
1 % acyclovir (micr.) (n=3)
1 % acyclovir (cryst.)(n=5)
Time (hours)
% Acyclovir release
0
5
10
15
20
25
0
10
20
30
40
50
60

Fig. 17

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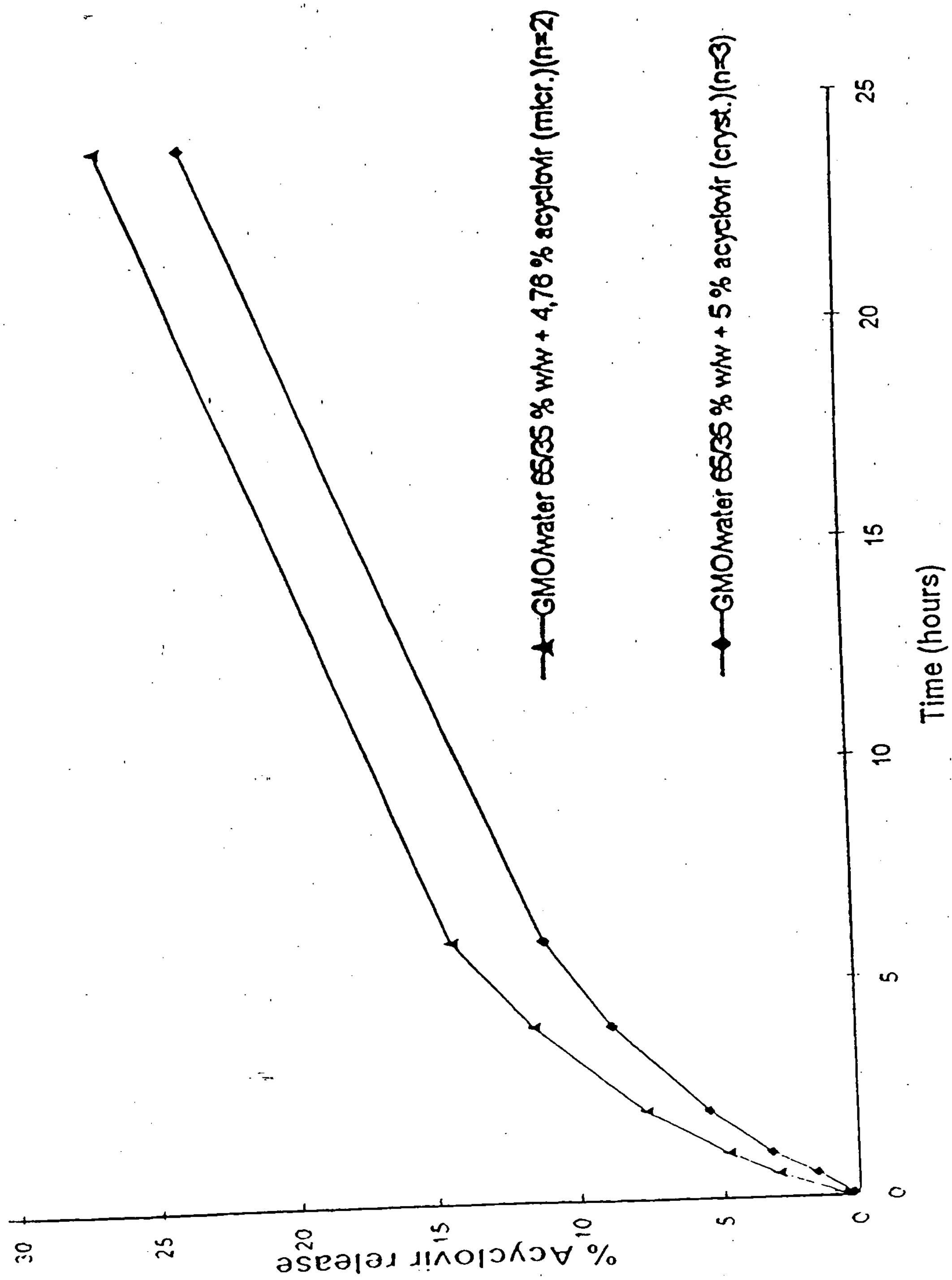

GMO/water 65/35 % w/w + 4,76 % acyclovir (mikr.)(n=2)
GMO/water 65/35 % w/w + 5 % acyclovir (cryst.)(n=3)
% Acyclovir release
Time (hours)
0
5
10
15
20
25
30

Fig. 18

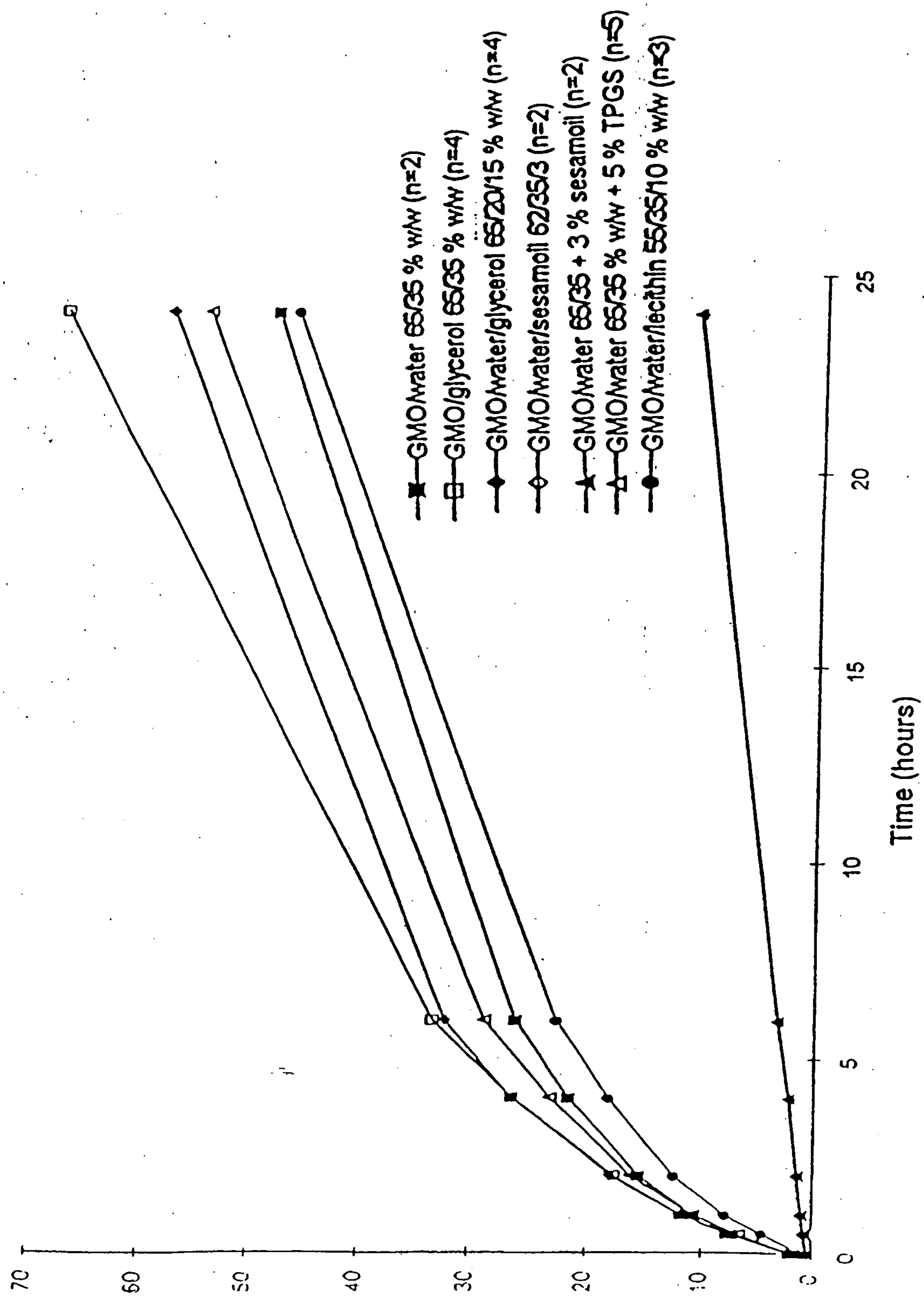

GMO/water 65/35 % w/w (n=2)
GMO/glycerol 65/35 % w/w (n=4)
GMO/water/glycerol 65/20/15 % w/w (n=4)
GMO/water/sesamoil 62/35/3 (n=2)
GMO/water 65/35 + 3 % sesamoil (n=2)
GMO/water 65/35 % w/w + 5 % TPGS (n=5)
GMO/water/lecithin 55/35/10 % w/w (n=3)
Time (hours)
0
5
10
15
20
25
% Acyclovir release
0
10
20
30
40
50
60
70

Fig. 19

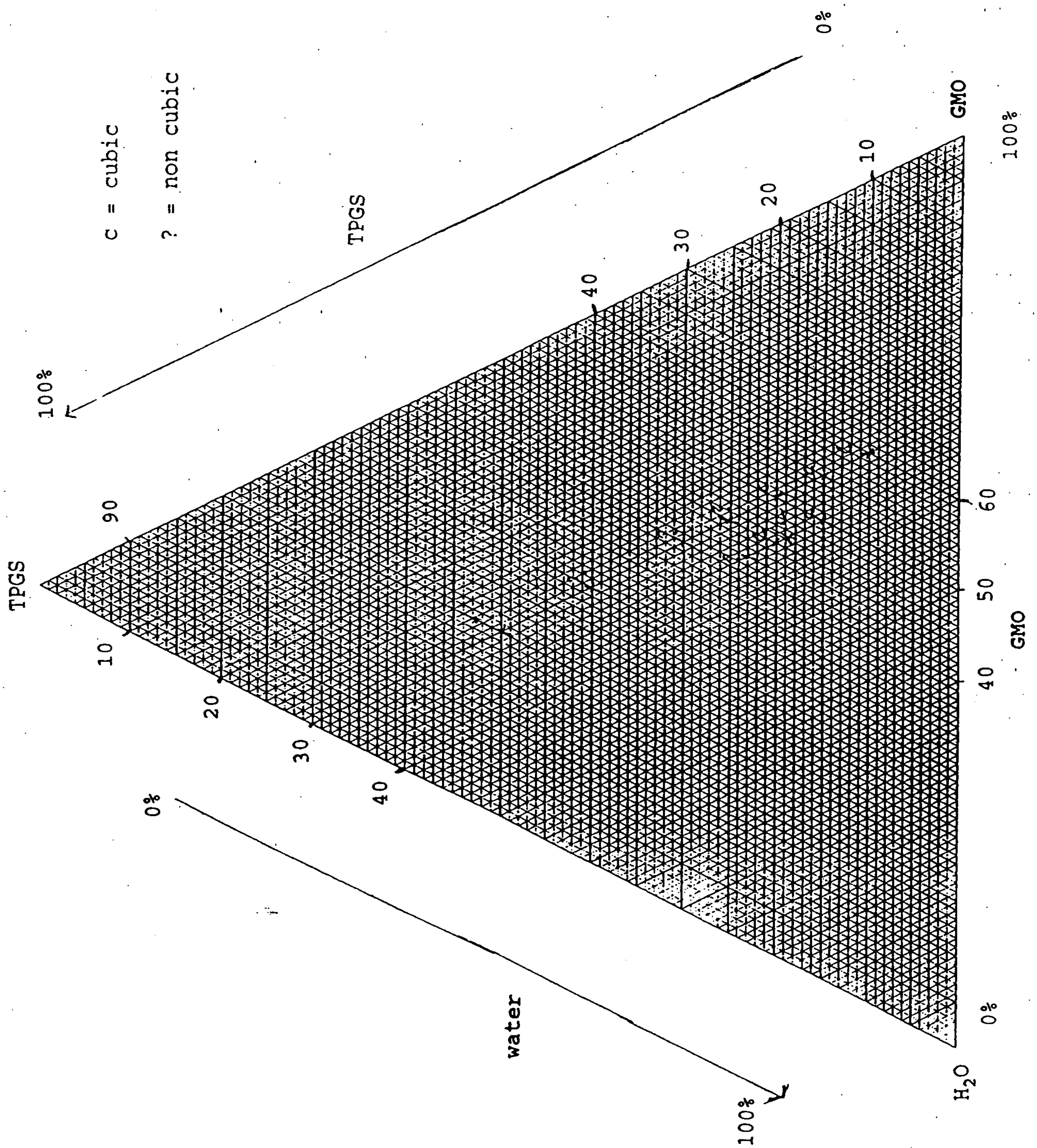
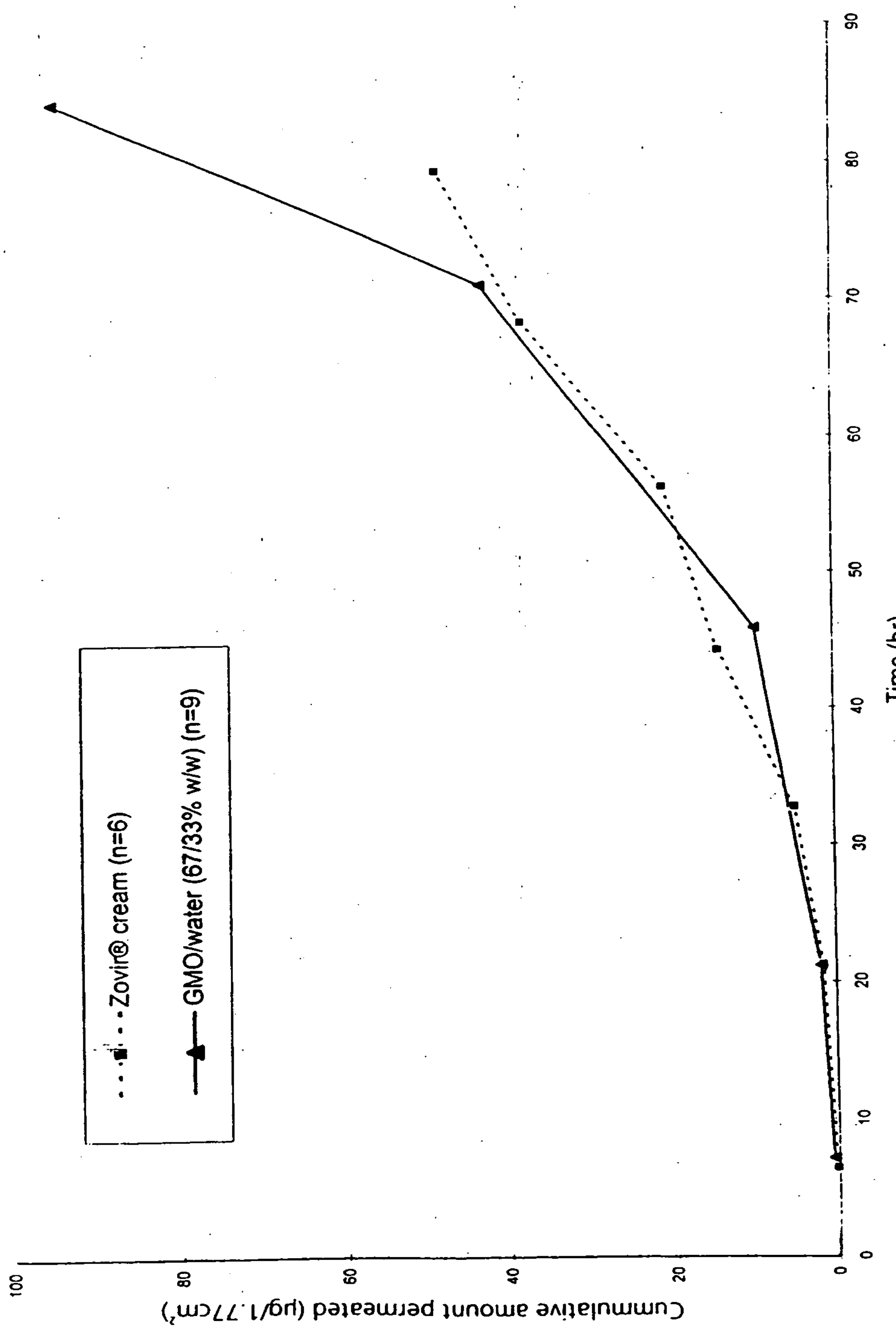

c = cubic
? = non cubic
TPGS
100%
0%
TPGS
90
10
20
30
40
GMO
100%
10
20
30
40
60
50
GMO
40
0%
water
100%
0%
H_2O

Fig. 20



Zovir® cream (n=6)
GMO/water (67/33% w/w) (n=9)
Time (hr)
0
10
20
30
40
50
60
70
80
90
Cummulative amount permeated (µg/1.77cm²)
0
20
40
60
80
100

Fig. 21

INTERNATIONAL SEARCH REPORT

Inte. .onal Application No
PCT/DK 98/00159

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/127

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
T	WO 97 13528 A (DUMEX-ALPHARMA) 17 April 1997 see page 64, line 17 - line 20 see page 65, line 13 - line 24 *document cited in the application* see figure 11 ---	1-115
A	WO 95 34287 A (GS DEVELOPMENT AB) 21 December 1995 see page 14; example 6 ---	1-115
A	WO 93 19736 A (KABI PHARMACIA AB) 14 October 1993 see the whole document ---	1-115
A	EP 0 429 224 A (THE PROCTER & GAMBLE COMPANY) 29 May 1991 see page 4; example 3 --- -/--	1-115

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 July 1998	31/07/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Benz, K

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/DK 98/00159

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	WO 95 31217 A (A/S DUMEX (DUMEX LTD.)) 23 November 1995 see claims 12-14 -----	51-56, 94-97

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/DK 98/00159

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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WO 9534287 A	21-12-1995	AU 2756395 A	05-01-1996
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		FI 944441 A	26-09-1994
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		US 5635205 A	03-06-1997
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		DK 429224 T	24-06-1996
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		FI 905682 A,B,	18-05-1991
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		IE 72515 B	23-04-1997
		JP 3209313 A	12-09-1991
		PT 95896 A,B	13-09-1991
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		CA 2189328 A	23-11-1995
		EP 0762896 A	19-03-1997
		FI 964583 A	15-11-1996
		NO 964832 A	13-01-1997